

AD_____

Award Number: DAMD17-02-1-0423

TITLE: Molecular Basis for the Toxicity of Schweinfurthins to
Breast Cancer Cells

PRINCIPAL INVESTIGATOR: Jeffrey Neighbors
David Wiemer, Ph.D.

CONTRACTING ORGANIZATION: University of Iowa
Iowa City, IA 52242

REPORT DATE: May 2005

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

20050826 102

REPORT DOCUMENTATION PAGEForm Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

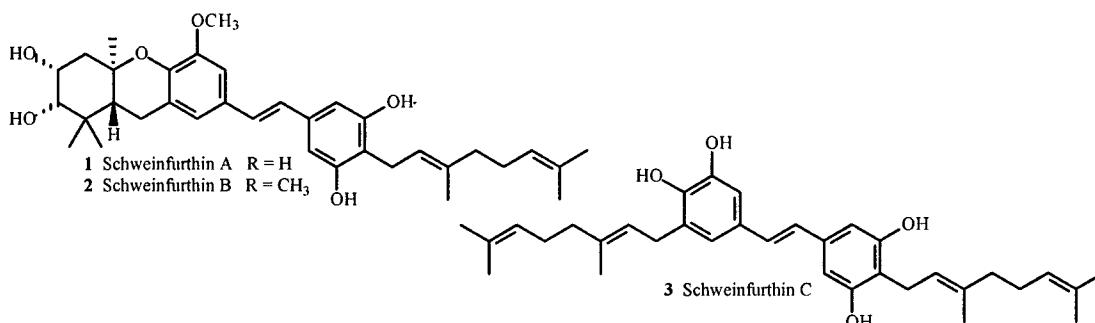
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE May 2005	3. REPORT TYPE AND DATES COVERED Annual Summary (18 Apr 2002 - 17 Apr 2005)	
4. TITLE AND SUBTITLE Molecular Basis for the Toxicity of Schweinfurthins to Breast Cancer Cells			5. FUNDING NUMBERS DAMD17-02-1-0423	
6. AUTHOR(S) Jeffrey Neighbors David Wiemer, Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Iowa Iowa City, IA 52242 E-Mail: Jeffrey-neighbors@uiowa.edu			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited				12b. DISTRIBUTION CODE
13. ABSTRACT (Maximum 200 Words) <p>The schweinfurthins are a small set of diprenylated stilbenes isolated from an African plant. Schweinfurthins A, and B display significant and unique activity in the NCI's 60 cell line panel, and the breast cancer lines MCF7 and HS 578T were among the most sensitive. We have developed multiple convergent routes to this family of compounds allowing an analog retaining anticancer activity to be synthesized as a single enantiomer. We have now synthesized a series of analogs including one bearing suitable functional groups for attachment to an affinity reagent or other reagent for determination of the mechanism of action. These studies have also led to synthetic analogs with more favorable stability, improving the ability to handle these agents. Quantitative structure activity studies have advanced our understanding of the essential pharmacophore and will pave the way for design of next generation analogs targeted at increasing the potency of the schweinfurthin family.</p>				
14. SUBJECT TERMS Schweinfurthin, natural products, drug development				15. NUMBER OF PAGES 62
				16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

Table of Contents

Cover.....	1
SF298.....	2
Introduction.....	4
Body.....	4
Key Accomplishments.....	8
Reportable Outcomes.....	8
Conclusions.....	9
References.....	9
Appendices.....	10

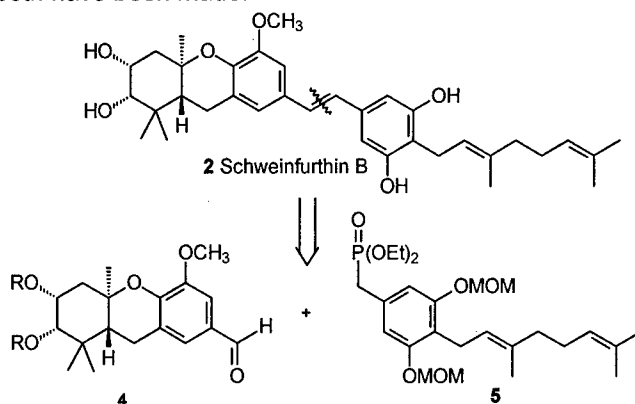
Introduction:

The schweinfurthins (**1–3**) are a small set of diprenylated stilbenes isolated from the African plant *Macaranga schweinfurthii* Pax. by Beutler *et al.* at the National Cancer Institute.^{1,2} Schweinfurthins A (**1**), B (**2**), display significant activity in the NCI's 60-cell line anticancer assay with average GI_{50} 's of less than 0.5 μ M. Among the most sensitive cell lines were the breast cancer lines MCF7 and HS 578T. Inspection of the spectrum of activity shows no correlation with any currently used agents suggesting that these compounds may act at a previously unrecognized target or through a novel mechanism. The schweinfurthins have been isolated in low and varying amounts from the natural source, and their absolute stereochemistry has yet to be elucidated. For these reasons, as well as their interesting biological activity, we have undertaken a total synthesis effort. An eventual asymmetric synthesis will allow assignment of the absolute stereochemistry and will provide a reliable source of schweinfurthins for further testing. Further chemical synthesis will eventually allow access to analogs designed to probe the biological activity of these compounds.



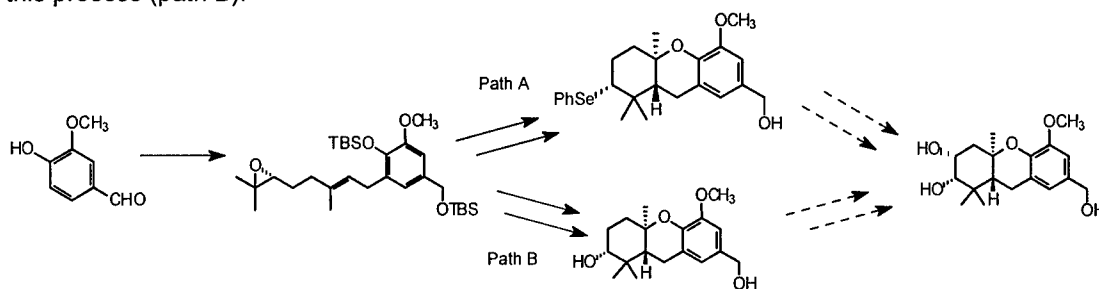
Body.

This project has been advanced considerably in this final year. We will discuss the most recent advances after a summary of the first two years has been described. Our overall strategy for the synthesis of the schweinfurthins envisioned penultimate construction of the central stilbene olefin via a Horner-Wadsworth-Emmons condensation. The project then required the synthesis of two fragments representing the left (**4**) and right halves (**5**) of the molecules. Important discoveries concerning both have been made.

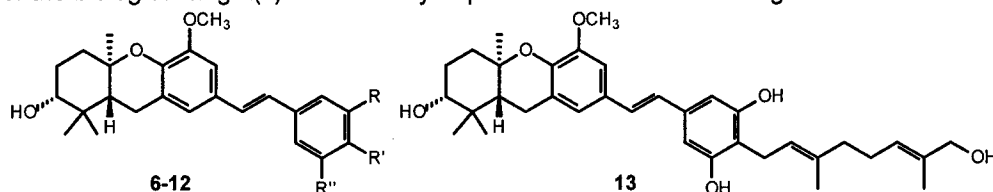


Our strategy for the synthesis of the left half of the molecule has evolved to include two cationic cascade cyclization sequences. Initially we explored a route wherein stereochemical information would be transferred into the cationic sequence through the agency of a phenylselenide moiety (path A). While successful at achieving a diastereoselective cascade cyclization,³ this intermediate proved intransigent to further modification consistent with our synthetic plans and we opted to explore a more biomimetic route. In this route an epoxide would

initiate the cationic sequence allowing direct installation of one of the A-ring hydroxyl groups in this process (path B).⁴



Using this second route we have synthesized 3-deoxyschweinfurthin B (**6**) and numerous analogs in enantioenriched form. The parent stilbene **6** of this series was found to have biological activity comparable to the natural products, and an examination of structure versus activity on this series has led to an appreciation of the role of the right half hydroxyl groups in the activity of these molecules.⁵ We have also used this left half to synthesize an active analog (**13**) with appropriate functionalization for attachment of affinity reagents. This will allow us to initiate a search for the biological target(s) of this family of potential breast cancer drug leads.

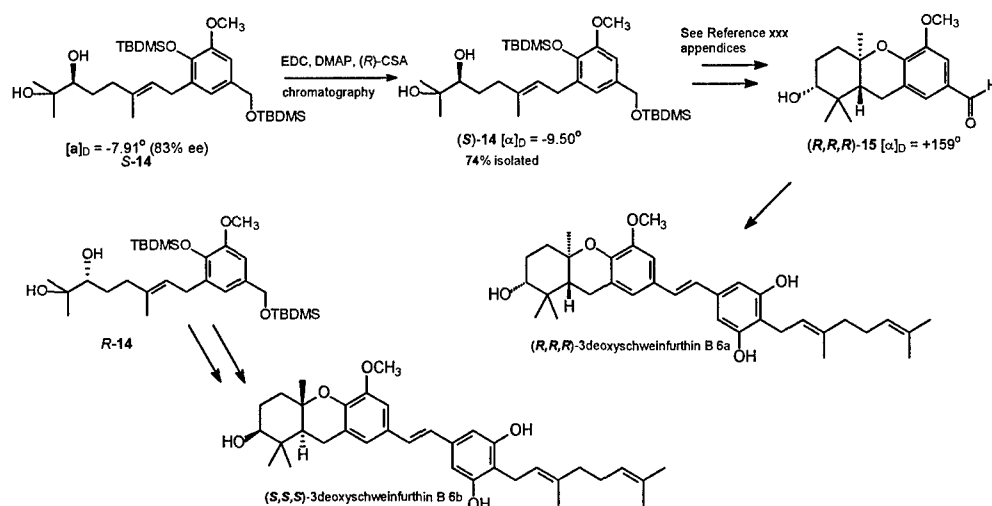


Compound	R	R'	R''	Mean GI ₅₀ 60 cell-line assay	Differential activity
6	OH	Geranyl	OH	0.2 μ M	Yes
7	OCH ₃	Geranyl	OCH ₃	6.6 μ M	Yes
8	F	Geranyl	F	43 μ M	Yes
9	H	Geranyl	H	19 μ M	No
10	H	H	H	16 μ M	No
11	OH	H	OH	7.8 μ M	Yes
12	OH	H	H	3.8 μ M	yes
13	OH	Geranyl-OH	OH	1.0 μ M	yes

Another important outcome of this SAR study is the finding of significant correlated activity in the phenol derivative **12**. Our collaborators had noted a disposition towards degradation in the natural products, and we surmised this would be due to oxidative lability of the resorcinol moiety. While the right half is clearly crucial to activity it appears that only one hydroxyl is absolutely required. This discovery should greatly facilitate further advances due to the increased stability.

Recent Advances

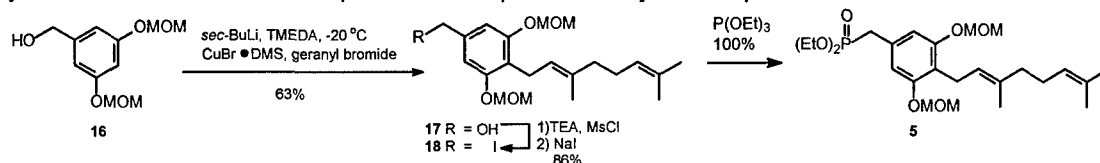
With this interesting structure-activity data in hand the next step was to achieve an enantioselective synthesis using our established route to secure samples of both enantiomers of 3-deoxyschweinfurthin B (**6**). After some experimentation it was discovered that allowing the



intermediate diol **14** to react with the appropriate enantiomer of camphorsulfonic acid under mixed anhydride esterification conditions allowed a kinetic resolution of the diol to be achieved. This has allowed both enantiomers of the arene **14** to be produced in >99% ee and subsequently both enantiomers of 3-deoxyschweinfurthin B (**6**) were synthesized and submitted to NCI for biological testing.

Intriguingly both enantiomers show strong anticancer activity (*R,R,R*-**6a** : mean GI_{50} = 0.62 μ M, *S,S,S*-**6b** : mean GI_{50} = 1.0 μ M). However the *R,R,R* isomer showed a high degree of correlation with the natural products, whereas the *S,S,S* isomer did not. This suggests that these agents may well act via two different mechanisms of action. From this point our attention will be focused on the *R,R,R* isomer as the most favorable for accessing the natural product stereochemistry.

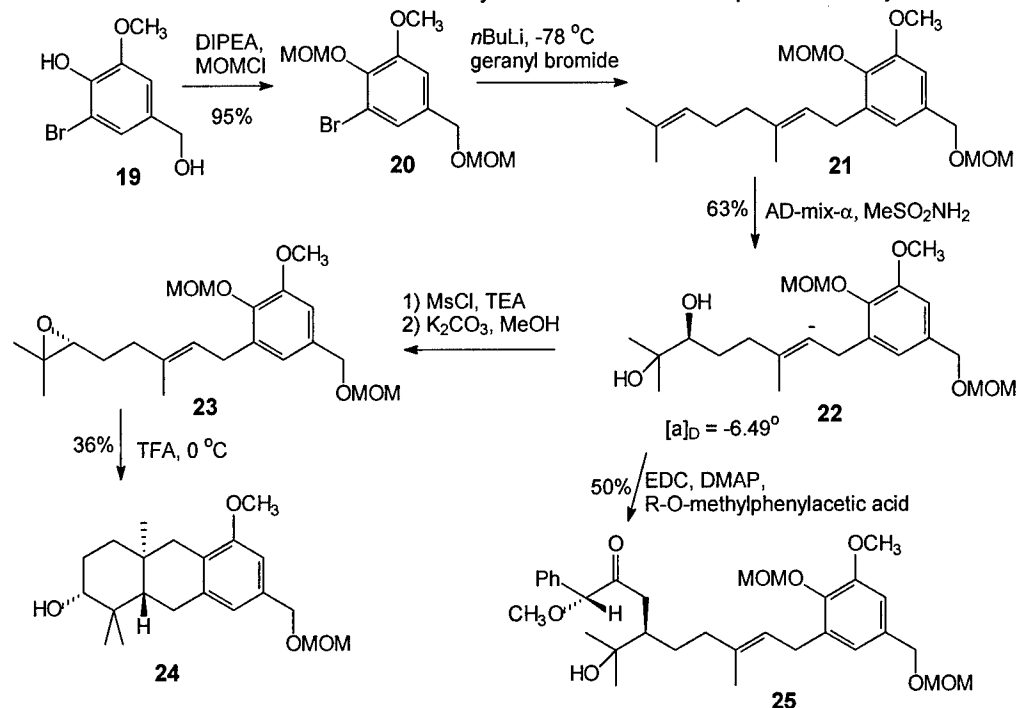
With all of these positive results we were now in the position to reexamine our synthetic efforts with an eye toward a more efficient synthesis. Our initial route to the right half phosphonate **5** at 8 steps and 34% overall yield seemed reasonable,⁶ but we wondered whether it might be possible to avoid the benzylic alcohol protection. After some exploration of conditions, direct alkylation of the benzylic alcohol **16** afforded the phosphonate **5** in 6 steps at comparable yields.⁷ This shortens the sequence to compounds **5** to just 6 steps.



Likewise the successful synthesis of the left half tricyclic aldehyde relied on a rather cumbersome protection deprotection sequence (See references 3 and 4, appendix). In this sequence a silyl ether was installed on the phenolic hydroxyl of bromide **19** only to be replaced with a ethoxyethyl (EE) group and then eventually reinstalled. This was an expeditious route and allowed us to avoid problems of retro-Brooke rearrangement of the silyl ether at one stage and the problems inherent in the resident asymmetric center in the EE protecting group at later stages.

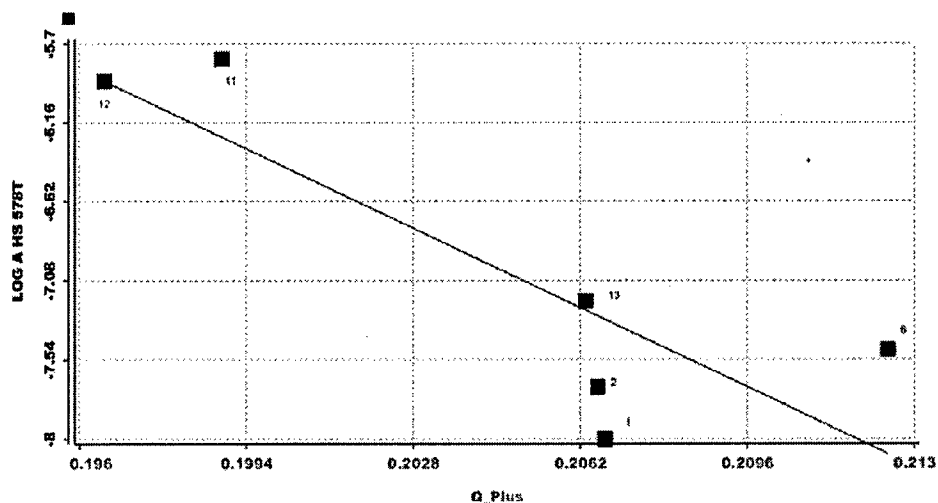
Prior to our recent work on this we had found that the retro-Brooke rearrangement could be avoided by use of a Stille coupling of a geranyl stannane and the aryl bromide **19**, however the desire to avoid the use of toxic stannanes led us to further exploration. Tactics involving the protection of both hydroxyl groups as methoxymethyl (MOM) ethers seemed a good place to start. Treatment of the aryl bromide with Hunig's Base and MOMCl gave a very high yield of the bis MOM protected arene which was then subjected to the halogen metal exchange conditions. The resulting geranylated arene **21** is then dihydroxylated asymmetrically and converted into the epoxide **23**. Absolute stereochemistry of the newly formed asymmetric center was determined by

¹H-NMR analysis of the ester **25** according to the methods of Trost and Mosher.⁸ Treatment with trifluoroacetic acid induces cationic cascade cyclization to afford the protected tricycle **24**.



This route to the protected tricycle **24** proceeds in 8 steps and 17% overall yield from vanillin. With comparable yields and 8 steps versus 14 in the original synthesis, this route is much more efficient to reach the tricycle stage. This second generation synthesis of the tricyclic hexahydroxanthene core will greatly facilitate further development of the schweinfurthin family as anticancer therapeutics.

Finally we have carried out quantitative structure activity relationship (QSAR) studies on the analogs with right half modifications synthesized to date. After searching for correlations with several common molecular descriptors calculated *in silico* (PM3 level of theory) we found a significant correlation ($r^2 = 0.72$, Gl₅₀ against HS 578T breast cancer cell line) with the Q-Plus (partial charge on the most positive atom in the molecule). The most positively charged atom



turned out to be the right half resorcinol hydroxyl hydrogen. This information is currently being used to design more potent analogs which should greatly improve the utility of these agents as drug leads and as biological probes.

Key Accomplishments.

- Second generation synthesis of the 3-deoxyschweinfurthin family has been achieved allowing much more facile access to these agents.
- The synthetic route has been expanded to establish an enantioselective synthesis and both enantiomers of the most active compound have been synthesized by a kinetic resolution approach and tested for anticancer activity.
- Analogs of 3-deoxyschweinfurthin B have been synthesized and QSAR studies carried out allowing identification of a strategy for improving potency in the family.
- An analog showing improved stability has been synthesized and shown to retain considerable activity.
- An analog with suitably placed functionality to attach an affinity reagent or for yeast three hybrid assays has been synthesized and shown to retain significant and differential bioactivity.

Reportable Outcomes.

Manuscript: A Cascade Cyclization Approach the Schweinfurthin B. Treadwell, E. M.; Neighbors, J. D.; Wiemer, D. F. *Org. Lett.* **2002**, 4, 3639-3642. (see appendix)

Manuscript: Neighbors, J. D.; Beutler, J. A.; Wiemer, D. F. An Epoxide-Initiated Cascade Cyclization Approach to the Schweinfurthins: Synthesis of 3-Deoxyschweinfurthin B. *J. Org. Chem.* **2005**, 70, 925-931. (see appendix)

Manuscript: Neighbors, J. D.; Salnikova, M. S.; Wiemer, D. F. Total synthesis of pawhuskin C: A dianion directed *ortho* metallation approach. *Tetrahedron Lett.* **2005**, 46, 1321-1324. (see appendix)

Manuscript: Neighbors, J. D.; Salnikova, M. S.; Beutler, J. A.; Wiemer, D. F. Synthesis and Structure Activity Studies of Schweinfurthin B Analogs: Evidence for the Importance of a Hydrogen Bond Donor in Expression of Differential Cytotoxicity. *J. Med. Chem.* In preparation (see appendix)

Abstract: Studies directed at the total synthesis of Schweinfurthin B. J. D. Neighbors, E. M. Treadwell, and D. F. Wiemer, 36th Great Lakes Regional ACS Meeting, Minneapolis, MN, June, 2002.

Abstract: Neighbors, Jeffrey D.; Wiemer, David F. A convergent approach to geranylated intermediates for synthesis of schweinfurthin B. Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003).

Abstract: Salnikova, Maya S.; Neighbors, Jeffrey D.; Wiemer, David F. Studies directed towards synthesis of schweinfurthin B analogs. Abstracts, 38th Midwest Regional Meeting of the American Chemical Society, Columbia, MO, United States, November 5-7 (2003)

Abstract: Neighbors, Jeffrey D.; Salnikova, M.; Wiemer, David F. Synthetic studies towards the schweinfurthin family of cytotoxins. Abstracts of Papers, 227th ACS National Meeting, Anaheim, CA, United States, March 28 – April 1, 2004.

Abstract: Neighbors, Jeffrey D.; Salnikova, Maya; Wiemer, David F.; Beutler, John B. 3-Deoxyschweinfurthin B: A synthetic schweinfurthin with anticancer activity. Abstracts, 39th Midwest Regional Meeting of the American Chemical Society, Manhattan, KS, United States, October 20-22, 2004.

Patent: Synthesis of Cytotoxic agent 3-deoxyschweinfurthin B. Patent pending United States and International

Conclusions.

We have developed a second generation synthesis to both intermediates required for our synthetic efforts. These new routes allow increased efficiency in producing analogs and in producing quantities available for further exploration. We have synthesized both enantiomers of the most active compound 3-deoxyschweinfurthin B and this has allowed us to determine that the *RRR* enantiomer has more highly correlated activity to that of the natural schweinfurthins. QSAR studies on analogs of this agent have given insight into the functionality essential to the activity of these agents. We have achieved the synthesis of analogs with greater stability and with functional groups suitable for attachment to affinity reagents both of which retain significant and correlated activity. Future efforts will focus on using our results to increase the potency of this family of potential anticancer agents further, as well as synthesizing quantities of affinity reagents for determination of the mechanism of action of these agents.

References.

1. Beutler, J. A.; Schoemaker, R. H.; Johnson, T.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 1509-1512.
2. Beutler, J. A.; Jato, J.; Cragg, G. M.; Boyd, M. R. *Nat. Prod. Lett.* **2000**, *14*, 349-404.
3. Treadwell, E. M.; Neighbors, J. D.; Wiemer, D. F. *Org. Lett.* **2002**, *4*, 3639-3642.
4. Neighbors, J. D.; Beutler, J. A.; Wiemer, D. F. An Epoxide-Initiated Cascade Cyclization Approach to the Schweinfurthins: Synthesis of 3-Deoxyschweinfurthin B. *J. Org. Chem.* **2005**, *70*, 925-931.
5. Neighbors, J. D.; Salnikova, M. S.; Beutler, J. A.; Wiemer, D. F. Synthesis and Structure Activity Studies of Schweinfurthin B Analogs: Evidence for the Importance of a Hydrogen Bond Donor in Expression of Differential Cytotoxicity. *J. Med. Chem.* In preparation
6. Treadwell, E. M.; Cermak, S. C.; Wiemer, D.F. *J. Org. Chem.* **1999**, *64*, 8718-8723.
7. Neighbors, J. D.; Salnikova, M. S.; Wiemer, D. F. Total synthesis of pawhuskin C: A dianion directed *ortho* metallation approach. *Tetrahedron Lett.* **2005**, *46*, 1321-1324.
8. a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519. b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370-2374.

Appendices.

1. Treadwell, E. M.; Neighbors, J. D.; Wiemer, D. F. *Org. Lett.* **2002**, *4*, 3639-3642.
2. Neighbors, J. D.; Beutler, J. A.; Wiemer, D. F. An Epoxide-Initiated Cascade Cyclization Approach to the Schweinfurthins: Synthesis of 3-Deoxyschweinfurthin B. *J. Org. Chem.* **2005**, *70*, 925-931.
3. Neighbors, J. D.; Salnikova, M. S.; Wiemer, D. F. Total synthesis of pawhuskin C: A dianion directed *ortho* metallation approach. *Tetrahedron Lett.* **2005**, *46*, 1321-1324
4. Neighbors, J. D.; Salnikova, M. S.; Beutler, J. A.; Wiemer, D. F. Synthesis and Structure Activity Studies of Schweinfurthin B Analogs: Evidence for the Importance of a Hydrogen Bond Donor in Expression of Differential Cytotoxicity. *J. Med. Chem.* In preparation

A Cascade Cyclization Approach to Schweinfurthin B

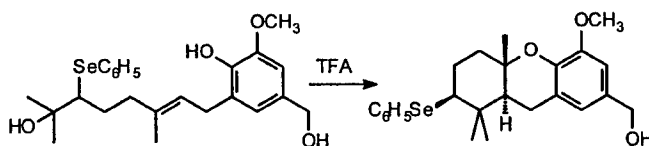
Edward M. Treadwell, Jeffrey D. Neighbors, and David F. Wiemer*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242

david-wiemer@uiowa.edu

Received July 30, 2002

ABSTRACT



A strategy for synthesis of the hexahydroxanthene moiety of the natural products schweinfurthin A, B, and D is described. The relative stereochemistry in the key cationic cyclization step is established through the preference of the phenylselenide substituent for an equatorial orientation.

The schweinfurthins (Figure 1, 1–4) are a small set of doubly prenylated stilbenes isolated from the African plant *Macaranga*

display significant activity in the NCI's 60-cell line anticancer assay with GI_{50} values less than $0.5 \mu M$.^{1,2} Their profile of activity does not match that of any clinically used anticancer agent, which suggests that these compounds may act either by a novel mechanism or at an unknown site. The schweinfurthins have been isolated in low and varying amounts from the natural source, and their absolute stereochemistry has yet to be elucidated. For these reasons, as well as their interesting biological activity, we have undertaken a total synthesis that ultimately should allow assignment of the schweinfurthins' absolute stereochemistry and provide a reliable source for further biological testing.

We have demonstrated the feasibility of a convergent approach to the schweinfurthins through synthesis of schweinfurthin C (3), the inactive congener.³ In that synthesis, the central stilbene olefin was prepared by a Horner–Wadsworth–Emmons condensation of a benzylic phosphonate (compound 5) and a complementary aldehyde. The phosphonate was prepared in eight steps from commercially available 3,5-dihydroxybenzoic acid (6) employing a directed ortho metalation for introduction of the geranyl substituent. Phosphonate 5 also could be used to advantage in preparation of the more complex schweinfurthins, provided preparation

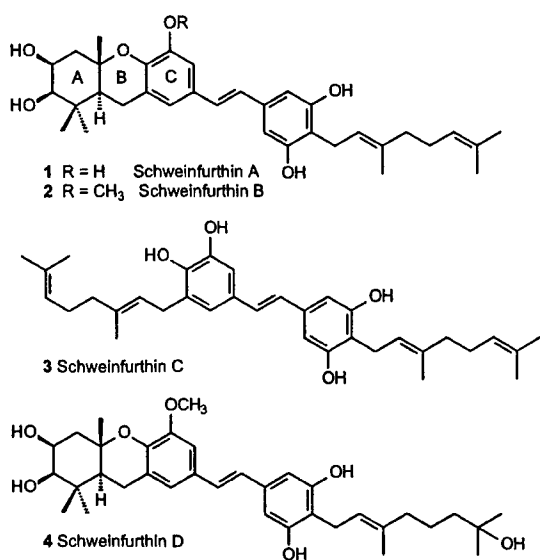


Figure 1. Structures of the schweinfurthins.

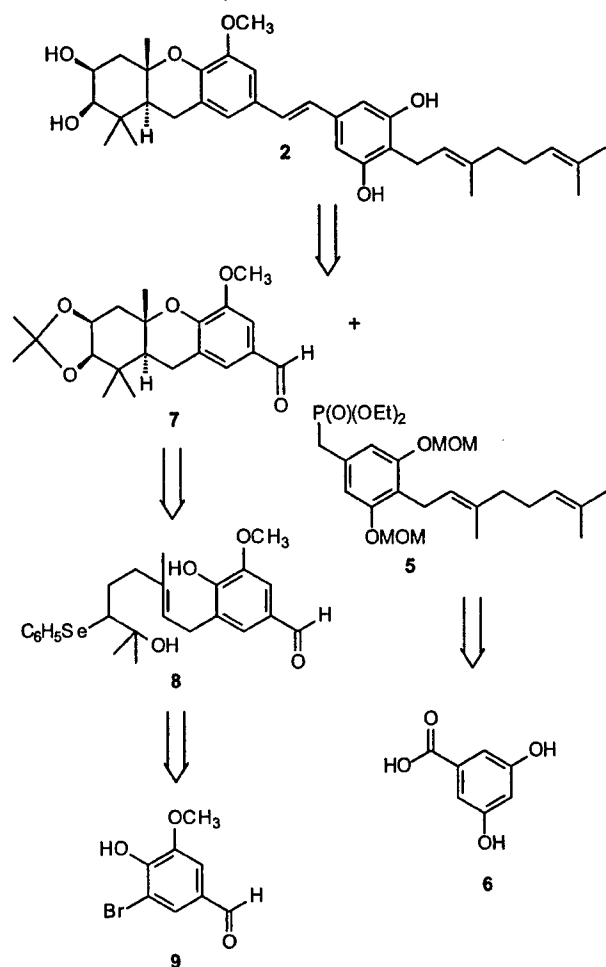
anga schweinfurthii Pax. by Beutler et al. at the National Cancer Institute. Schweinfurthins A (1), B (2), and D (4)

(1) Beutler, J. A.; Shoemaker, R. H.; Johnson, T.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 1509–1512.

(2) Beutler, J. A.; Jato, J.; Cragg, G. M.; Boyd, M. R. *Nat. Prod. Lett.* **2000**, *14*, 399–404.

(3) Treadwell, E. M.; Cermak, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718–8723 and references therein.

Scheme 1. Retrosynthetic Analysis of Schweinfurthin B



of a tricyclic aldehyde (7, Scheme 1) could be achieved. The methylated version of this tricyclic aldehyde was targeted initially because the requisite phenolic methyl ether could be carried along the sequence from the aromatic starting material, bromovanillin 9.

One approach to the hexahydroxanthene core could be based on an acid-catalyzed cyclization to assemble both the A- and B-rings on an aromatic C-ring in a single reaction. Previous reports on cyclizations of geranylated phenols are known, but often the cyclizations occurred in low yield with numerous byproducts observed.^{4,5} We hypothesized that a substituent α to the incipient carbocation could help stabilize the terminal cation, thereby possibly increasing the yield and providing an opportunity for stereocontrol. There is substantial precedent for stabilization of adjacent cations by phenylthio substituents, and some precedent for stabilization by phenylselenenyl groups.⁶ As shown in Figure 2, one transition state would place the phenylselenenyl substituent in an equatorial position with a pseudochair conformation in the incipient B-ring, while the other would require an axial phenylselenenyl group with a pseudoboat conformation. The use of hydroxyselenenides for similar reactions has been described in two seminal papers by Kametani et al., though

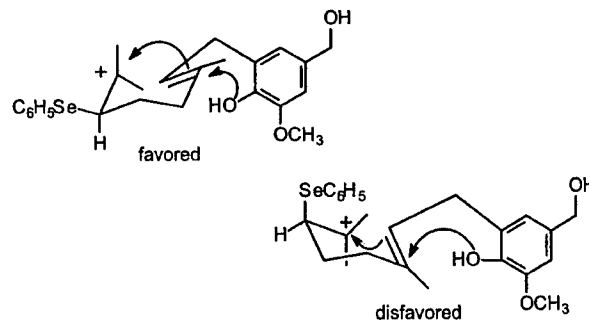
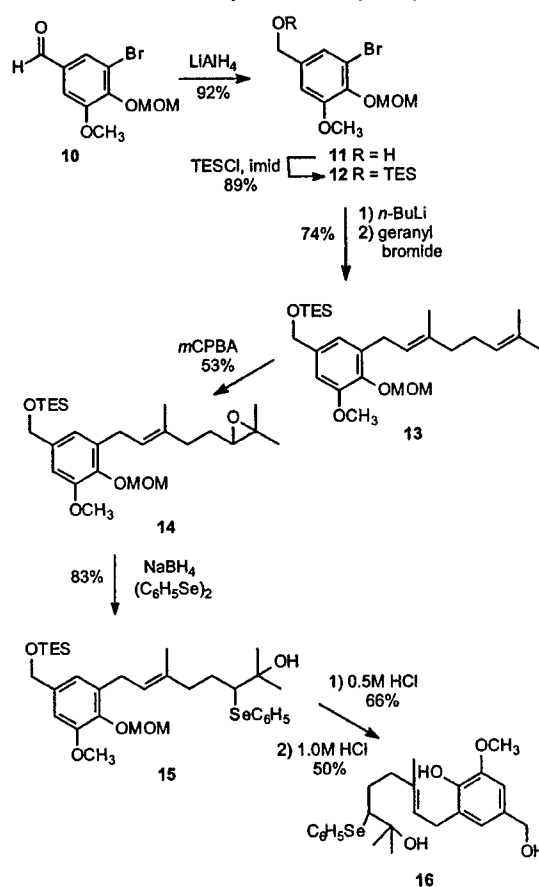


Figure 2. Possible transition states for cyclization of hydroxyselenide 8.

application to enantiopure material was not attempted.⁷ With this aim in mind, racemic β -hydroxyselenide 8 was viewed as a cyclization precursor that would allow evaluation of the viability of such an approach.

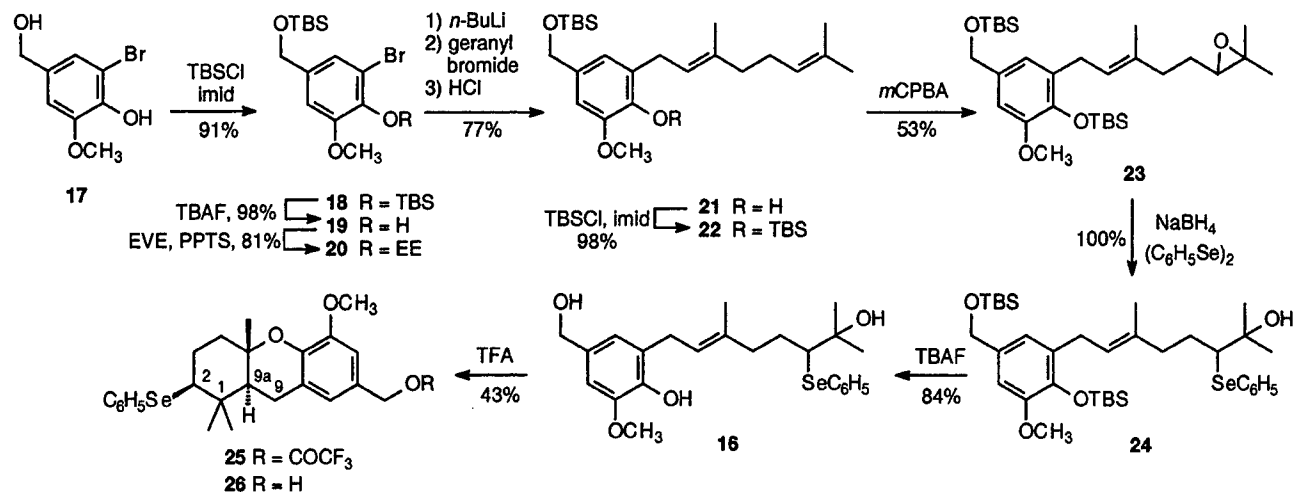
The synthesis began with preparation of the known benzaldehyde derivative 10⁸ (Scheme 2) from commercially

Scheme 2. Initial Synthesis of Hydroxyselenide 16



available vanillin. Reduction of the aldehyde and subsequent protection of the alcohol as the triethylsilyl ether afforded

Scheme 3. Revised Synthesis of Hydroxyselenide 16



the fully protected arene 12, and halogen–metal exchange followed by reaction with geranyl bromide allowed installation of the geranyl chain in 74% yield. An *m*CPBA epoxidation of compound 13 initially afforded a 1:1 mixture of the regioisomeric 6,7- and 2,3-epoxides in 55% yield along with the diepoxide (7%). Even though careful column chromatography could separate the two regioisomers, the low yield of the desired product was unattractive. When the reaction was conducted at lower temperatures with slow addition of the oxidant, the yield of the desired 6,7-epoxide 14 increased to 53% along with only 8% of the 2,3-epoxide and significant recovery of the starting material (32%). Epoxide 14 reacted smoothly with phenylselenide anion generated in situ⁹ to give the hydroxyselenide 15 in 83% yield.

The only transformations remaining prior to cyclization were removal of the two protecting groups, but in the best case scenario this was done through a two-step procedure. Initial treatment with 0.5 M HCl hydrolyzed the silyl ether, and subsequent treatment with 1.0 M HCl hydrolyzed the MOM acetal in an overall yield of 33%. Despite numerous attempts, all efforts at removing both protecting groups in a single step gave either incomplete deprotection or lower yields with greater byproduct formation.

A second synthetic strategy was developed to address this problematic deprotection issue. Because the silyl ether could be readily removed, it appeared attractive to protect the phenolic functionality as a silyl ether as well. However, introduction of the phenolic silyl ether would have to follow the alkylation step in the synthetic sequence, because migration of the silyl group from the oxygen to the adjacent ortho carbon has been observed in similar reactions.¹⁰ Therefore, an ethoxyethyl-protected phenol was envisioned for the sequence up to and including the alkylation step, at which point it would be removed and a silyl ether installed in its place.¹¹

Direct protection of the phenol as the ethoxyethyl ether was not successful under acidic conditions, so an indirect route was employed. The known alcohol 17,¹² also available from vanillin, was disilylated and then selectively cleaved to the free phenol 19 by treatment with 1.0 equiv of tetrabutylammonium fluoride¹³ (Scheme 3). An acid-catalyzed reaction of compound 19 with ethyl vinyl ether gave the fully protected aryl bromide 20. This intermediate can be prepared in multigram quantities in an overall yield of 68% from vanillin without need for a chromatographic separation. Application of the halogen–metal exchange protocol and reaction with geranyl bromide afforded the analogous geranylated arene, which upon acidic workup gave the free phenol 21. After silylation of the free phenol, the material was subjected to oxidation, and epoxide opening analogous to that used on arene 13 delivered the protected α -hydroxyselenide 24. The deprotected target 16 could be obtained in 84% yield by treatment of the disilylated material with excess TBAF.

(4) (a) Barua, A. K.; Banerjee, S. K.; Basak, A.; Bose, P. K. *J. Indian Chem. Soc.* **1976**, *53*, 638–639. (b) Manners, G.; Jurd, L.; Stevens, K. *Tetrahedron* **1972**, *28*, 2949–2959. (c) Trammell, G. L. *Tetrahedron Lett.* **1978**, 1525–1528.

(5) Mechoulam and Yagen have reported cyclization of geranylolivetol in 88% yield, but this required heating with concentrated H_2SO_4 in nitromethane. Mechoulam, R.; Yagen, B. *Tetrahedron Lett.* **1969**, 5349–5352.

(6) (a) For a review, cf.: Harring, S. R.; Edstrom, E. D.; Livinghouse, T. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, H. W., Ed.; Jai Press: Greenwich, CT, 1992; Vol 2., pp 299–376. For more recent examples, cf.: (b) Branchaud, B. P.; Blanchette, H. S. *Tetrahedron Lett.* **2002**, *43*, 351–353. (c) Toshimitsu, A.; Hirose, C.; Tamao, K. *Synlett* **1996**, 465–467 and references therein.

(7) (a) Kametani, T.; Suzuki, K.; Kurobe, H.; Nemoto, H. *J. Chem. Soc., Chem. Commun.* **1979**, 1128–1129. (b) Kametani, T.; Kurobe, H.; Nemoto, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1085–87.

(8) Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1991**, *56*, 2115–2122.

(9) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697–2699.

(10) When treated with *n*-butyllithium, both compound 18 and the TIPS analogue show a 1,3 O–C silyl migration in the only isolable products.

(11) The EE group was not carried throughout the sequence to avoid introduction of diastereomers and because the phenolic EE group was readily cleaved upon silica gel column chromatography.

(12) (a) Brink, M. *Acta Chem. Scand.* **1965**, *19*, 255–256. (b) Claus, P.; Schilling, P.; Gratzl, J. S.; Kratzl, K. *Monatsh. Chem.* **1972**, *103*, 1178–1193.

(13) Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681–684.

To induce the desired cationic cyclization, the tertiary alcohol **16** was treated with acid under various conditions. Treatment of compound **16** with TFA afforded a single hexahydroxanthene system as the labile trifluoroacetate **25**. Purification of this product by column chromatography gave both the trifluoroacetate **25** and the parent alcohol **26** in 43% combined yield.

The relative stereochemistry of the hexahydroxanthene was assigned after extensive NMR spectroscopy on the trifluoroacetate **25**. Analysis of the coupling constants observed for the C-2 hydrogen (schweinfurthin numbering) suggested an axial disposition and hence an equatorial orientation for the phenylselenide group. The bridgehead methine hydrogen (C-9a) also appeared to be in an axial orientation on the basis of analysis of the coupling constants with the benzylic hydrogens at C-9. In this case, a COSY spectrum nicely displayed the H-9_{ax}, H-9_{eq}, H-9a spin system, indicative of a *trans*-decalin skeleton. Furthermore, the chemical shifts of the methyl groups compared favorably to those reported for a related *trans*-fused system but did not agree with those of a related *cis*-fused structure.¹⁴ Finally, a NOESY spectrum revealed correlations (Figure 3) of the bridgehead methyl group with axial hydrogens at C-3 and C-9 and to the axial methyl group at C-1. On the other face of the molecule, complementary correlations were observed between the equatorial methyl group at C-1 and the axial hydrogen at C-9a, as well as from the axial hydrogen at C-2 to both the C-1 equatorial methyl group and the C-9 equatorial hydrogen.

The NMR data make clear that the phenylselenide substituent was successful in providing a single diastereomer of the hexahydroxanthene and may facilitate the cyclization. The equatorial disposition of the phenylselenide moiety in the final product is encouraging in that this single substituent appears to effectively govern the stereochemistry of the

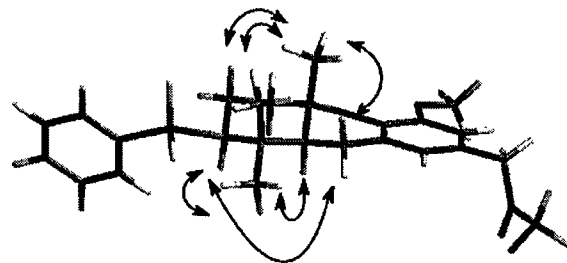


Figure 3. Selected NOESY correlations for compound **25** shown on a SPARTAN minimized structure (PM3 level).

bridgehead centers, as expected from consideration of the transition states (Figure 2).

Preparation of the tricycle **26** should allow elaboration of racemic schweinfurthin B after introduction of the A-ring hydroxyl groups and coupling with phosphonate **5**. Alternatively, now that the viability of this cyclization strategy has been shown, preparation of the epoxide **23** in nonracemic form should allow preparation of nonracemic schweinfurthin B (**2**). Our efforts to prepare the nonracemic epoxide, as well as to complete preparation of the natural products themselves, will be reported in due course.

Acknowledgment. Financial support from the DOD Breast Cancer Research Program (DAMD17-01-1-0276 and DAMD17-02-1-0423) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data for compounds **16**–**26**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0266368

(14) Rouessac, A.; Rouessac, F. *Tetrahedron* **1987**, *37*, 4165–4170.

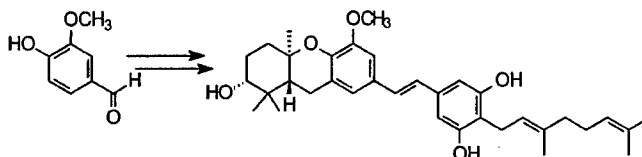
Synthesis of Nonracemic 3-Deoxyschweinfurthin B

Jeffrey D. Neighbors,[†] John A. Beutler,[‡] and David F. Wiemer^{*,†}

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242-1294, and Molecular Targets Development Program, Center for Cancer Research, National Cancer Institute, Frederick, Maryland 21702

david-wiemer@uiowa.edu

Received September 3, 2004



Synthesis of nonracemic 3-deoxyschweinfurthin B has been accomplished through a synthetic sequence including a key cascade cyclization of an epoxy olefin. The intermediate epoxide could be prepared as a single enantiomer through an AD-mix- α (or AD-mix- β) oxidation, and the stereochemistry of the epoxide has been shown to control formation of the two additional stereogenic centers created through the cyclization. Synthetic 3-deoxyschweinfurthin B was found to have potent differential activity in the National Cancer Institute's 60 cell line anticancer assay. This represents the first synthesis of the tetracyclic schweinfurthin skeleton, validating our overall synthetic strategy and providing the first schweinfurthin analogue with activity slightly greater than those of the natural products.

At this time, the small family of natural products known as the schweinfurthins is composed of four compounds (Figure 1, 1–4) isolated from the African plant *Macaranga schweinfurthii* Pax at the National Cancer Institute.^{1,2} Schweinfurthins A (1), B (2), and D (4) display significant activity in the National Cancer Institute's (NCI's) 60 cell line anticancer assay with mean GI₅₀ values <1 μ M. Their biological activity has attracted interest because some central nervous system, renal, and breast cancer cell lines are among the types most sensitive to these compounds. Furthermore, the spectrum of their anticancer activity shows no correlation with any currently used agent and suggests that these compounds may be acting at a previously unrecognized target or through a novel mechanism. Repeated attempts to isolate larger samples of the schweinfurthins from the natural source have met with limited success, and the absolute stereochemistry of these natural products has yet to be determined. For these reasons, as well as their interesting biological activity, we have undertaken an effort directed at total synthesis of the schweinfurthins. An

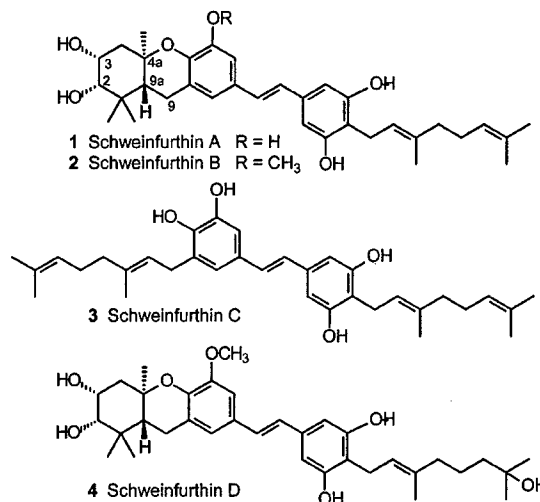


FIGURE 1. Natural schweinfurthins.

asymmetric synthesis would be particularly attractive because it would allow assignment of the absolute stereochemistry of the natural products and could provide a reliable source of natural schweinfurthins and synthetic analogues for further biological testing.

Our retrosynthetic analysis of schweinfurthin B (Figure 2) calls for an approach where the central stilbene olefin would be constructed in the penultimate step. This

* To whom correspondence should be addressed. Phone: (319) 335-1365. Fax: (319) 335-1270.

[†] University of Iowa.

[‡] National Cancer Institute.

(1) Beutler, J. A.; Shoemaker, R. H.; Johnson, T.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 1509–1512.

(2) Beutler, J. A.; Jato, J.; Cragg, G. M.; Boyd, M. R. *Nat. Prod. Lett.* **2000**, *14*, 349–404.

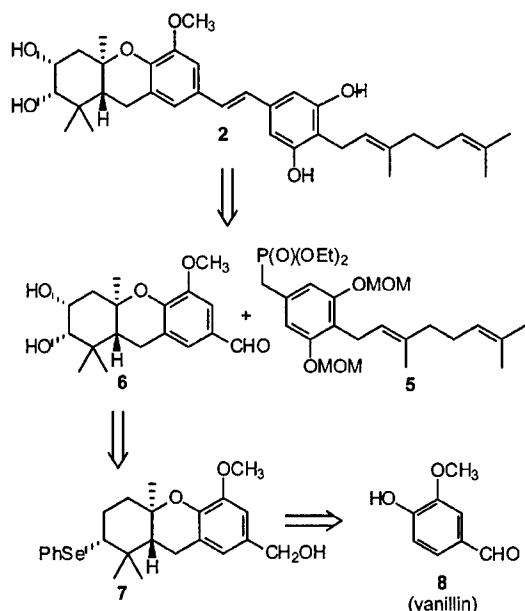
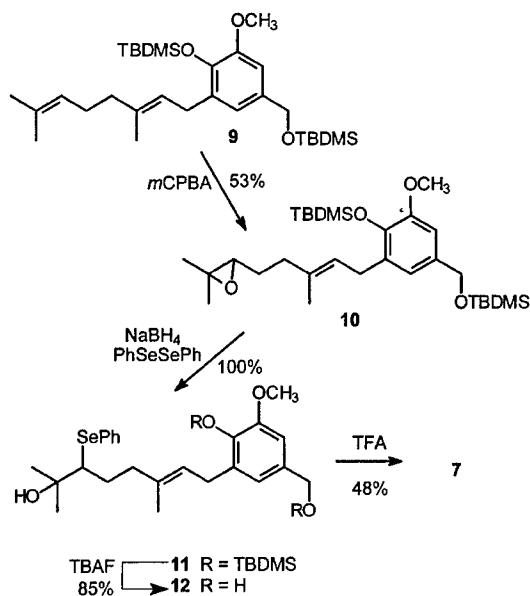


FIGURE 2. Retrosynthetic analysis.

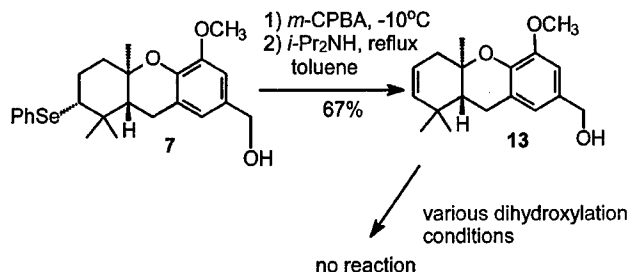
SCHEME 1



approach is highly convergent and should allow facile access to analogues for structure–activity studies. We already have demonstrated that a Horner–Wadsworth–Emmons (HWE) condensation can be used to introduce the stilbene olefin through synthesis of the simplest member of the family, schweinfurthin C (3),³ and the “right-half” phosphonate (5) employed in that endeavor can be conserved for synthesis of schweinfurthins A and/or B. All of the tetracyclic schweinfurthins require a dihydroxylated “left-half” core represented in the aldehyde 6. A synthetic approach to phenyl selenide 7 (Scheme 1), which can be viewed as an advanced precursor to this aldehyde, has been reported in a previous

(3) Treadwell, E. M.; Cermak, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718–8723.

SCHEME 2



paper.⁴ Schweinfurthin B (2) was chosen as the initial target so recourse could be made to commercial vanillin as a starting material. This would forego the need for an orthogonal protection of the aryl oxygens because the regiochemistry of the required methyl ether is secured.

Our initial route to racemic hexahydroxanthene 7 involved epoxidation of the geranyl arene 9, available from vanillin in 60% yield over seven steps.⁴ The epoxide 10 was opened to phenyl selenide 11, which, after deprotection and acid-catalyzed cationic cascade cyclization, afforded a single racemic diastereomer of the *trans*-fused tricycle 7. Completion of the natural product from this point would require selenoxide elimination, dihydroxylation of the resulting olefin, and an HWE condensation of the aldehyde with the phosphonate encompassing schweinfurthin's right half (*vide supra*). In the event, oxidation of racemic phenyl selenide 7 with *m*-CPBA and thermal elimination of the resulting selenoxide gave the olefin 13 (Scheme 2) in moderate yield.⁵ Despite some literature precedent for similar oxidation/elimination reactions under mild reaction conditions, it was necessary to subject this system to a more forceful protocol.^{6,7} In this case, the decreased flexibility of the tricyclic system may make it difficult to achieve the *syn* conformation of the selenoxide and the adjacent hydrogen necessary for elimination.

With olefin 13 in hand, introduction of the diol moiety through an osmium-mediated dihydroxylation reaction was examined. Inspection of a molecular model of olefin 13 showed that both faces might be somewhat inaccessible, and that if reaction occurred it would most likely take place from the undesired face of the olefin *trans* to the angular methyl group. Despite this analysis, there is literature precedent for dihydroxylation in similar systems,⁸ and both diastereomers of the *cis*-diol would be of use from a structure–activity standpoint. Unfortunately, treatment of olefin 13 with catalytic or stoichiometric osmium tetroxide or potassium osmate failed to give any detectable dihydroxylation products in our hands.⁹

(4) Treadwell, E. M.; Neighbors, J. D.; Wiemer, D. F. *Org. Lett.* **2002**, *4*, 3639–3642.

(5) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelburn, D. F. *J. Org. Chem.* **1978**, *43*, 1697–1705.

(6) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447.

(7) It was found that yields increased for the elimination when going from the original conditions of Reich (refluxing dichloromethane) to benzene and finally toluene.

(8) (a) McMurray, J. E.; Erion, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 2712–2720. (b) Mori, K.; Komatsu, M. *Liebigs Ann. Chem.* **1988**, 107–119.

(9) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421–433.

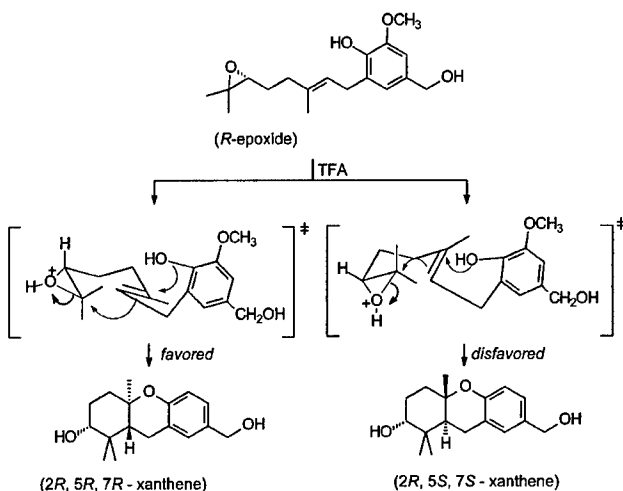
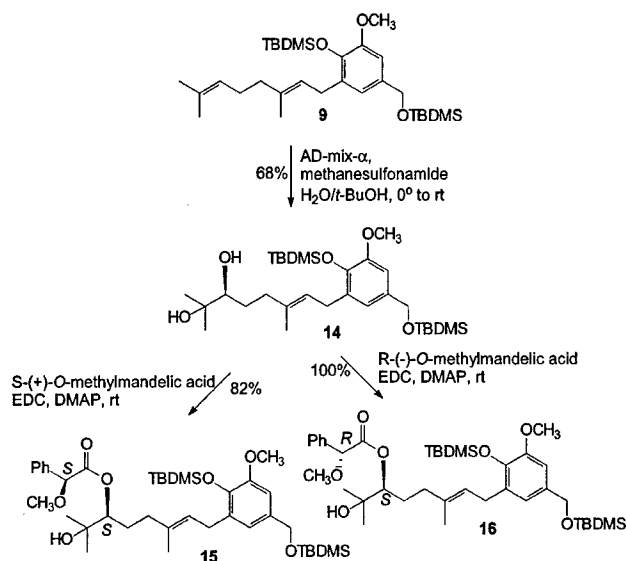


FIGURE 3. Proposed path of epoxide cyclization.

The risk of an adverse stereochemical outcome of the dihydroxylation and the difficult oxidation observed in practice made it necessary to seek alternative methodology for introduction of functionality in the A ring of the tricycle. The pioneering work of van Tamelen¹⁰ and Corey¹¹ on biogenic cyclization of oxidosqualene, and subsequently on acid-catalyzed cyclization of synthetic equivalents, suggested that a nonracemic epoxide (Figure 3) could serve as a viable substrate for cyclization. Perusal of the literature shows numerous examples of protic and Lewis acid-catalyzed epoxyolefin cyclizations.¹² In this system, a pseudo-chair–chair-like transition state terminated through capture of the tertiary cation by the phenolic oxygen would afford the desired *trans*-fused xanthene. If a pseudoequatorial disposition of the epoxide moiety were favored, then cyclization of the (*R*)-epoxide could be predicted to favor the (2*R*,5*R*,7*R*)-diastereomer of the resulting tricycle, as shown. This strategy could lead directly to 3-deoxyschweinfurthin B, and in principle further elaboration of the A-ring could lead to the natural product.

There is considerable literature precedent for regioselective dihydroxylation of the terminal olefin in geraniol itself,¹³ and it appeared that the steric encumbrance and electronic effects in a geranyl arene would favor parallel regiocontrol. The resulting diol might then be converted

SCHEME 3



to the epoxide via the secondary mesylate,¹⁴ to intersect the route already developed⁴ or bring new functionality into the tricyclic system. To our delight, treatment of diene **9** with AD-mix- α in the presence of methanesulfonamide gave the desired diol **14** in 68% yield and 83% ee (Scheme 3). Use of the pictorial device suggested by Sharpless et al.¹⁵ for the facial selectivity of the attack indicated that an (*S*)-alcohol should be expected at the newly created asymmetric center.

While the stereochemistry at the new stereogenic center was assigned tentatively as *S*, a spectroscopic method to support an assignment was pursued.¹⁶ In this case, separate samples of the enantioenriched diol **14** were treated with the (*S*)- and (*R*)-enantiomers of *O*-methylmandelic acid under standard mixed anhydride coupling conditions. After isolation of the major diastereomer from each reaction, compounds **15** and **16**, respectively, the ¹H NMR spectra were examined for chemical shift differences in accordance with the model of Trost et al.^{16b} Significant shifts were noted for two sets of easily identifiable hydrogens in the two diastereomers (Figure 4). The terminal methyl groups are found as a singlet with a chemical shift of 1.16 ppm in ester **16** and are shifted to 0.94 ppm in isomer **15**. In contrast, the olefinic hydrogen is shifted from 5.27 ppm in compound **15** to a more upfield 5.00 ppm in the isomer **16**. Both of these changes are consistent with expectations based on placing the more upfield hydrogens in the shielding region of the phenyl ring when viewed in an extended Newman projection format as required by the Trost model.^{16b} On this basis, the new asymmetric center in diol **14** was assigned the *S* configuration.

(10) (a) van Tamelen, E. E.; Willet, J. D.; Clayton, R. B.; Lord, K. E. *J. Am. Chem. Soc.* **1966**, *88*, 4752–4754. (b) Willet, J. D.; Sharpless, K. B.; Lord, K. E.; van Tamelen, E. E.; Clayton, R. B. *J. Biol. Chem.* **1967**, *242*, 4181–4191.

(11) Corey, E. J.; Russey, W. E.; Ortiz de Motellano, P. R. *J. Am. Chem. Soc.* **1966**, *88*, 4750–4751.

(12) (a) Sharpless, K. B. *J. Am. Chem. Soc.* **1970**, *92*, 6999–7001. (b) van Tamelen, E. E.; Holton, R. A.; Hopla, R. E.; Kouz, W. E. *J. Am. Chem. Soc.* **1972**, *94*, 8228–8229. (c) van Tamelen, E. E.; Anderson, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 8225–8228. (d) van Tamelen, E. E.; Seiler, M. P.; Wierenga, W. J. *J. Am. Chem. Soc.* **1972**, *94*, 8229–8231. (e) Tanis, S. P.; Herrington, P. M. *J. Org. Chem.* **1983**, *48*, 4572–4580. (f) Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005–7008. (g) Fish, P. V.; Sudhakar, A. R.; Johnson, W. S. *Tetrahedron Lett.* **1993**, *34*, 7849–7852. (h) Sen, S. E.; Zhang, Y. Z.; Smith, S. M.; Huffman, J. C. *J. Org. Chem.* **1998**, *63*, 4459–4465. (i) Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526–3527. (j) Sen, S. E.; Roach, S. L.; Smith, S. M.; Zhang, Y. Z. *Tetrahedron Lett.* **1998**, *39*, 3969–3972.

(13) (a) Corey, E. J.; Zhang, J. *Org. Lett.* **2001**, *3*, 3211–3214. (b) Vidari, G.; Dapiaggi, A.; Zanoni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485–6488. (c) Zhang, X.; Archelas, A.; Meou, A.; Furstoss, R. *Tetrahedron: Asymmetry* **1991**, *2*, 247–250.

(14) For examples, see: (a) Rickards, R. W.; Thomas, R. D. *Tetrahedron Lett.* **1993**, *34*, 8369–8372. (b) McMurray, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942–6949. (c) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999–10003.

(15) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, X.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771.

(16) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374. (c) For application to an extended alicyclic system, see, for example: Gallinis, D. L.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 7804–7807.

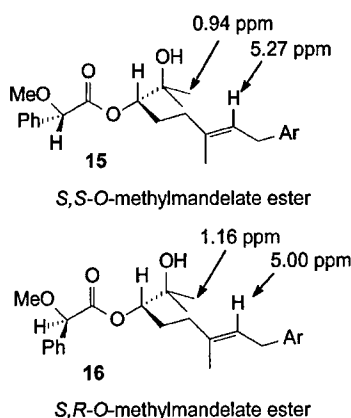
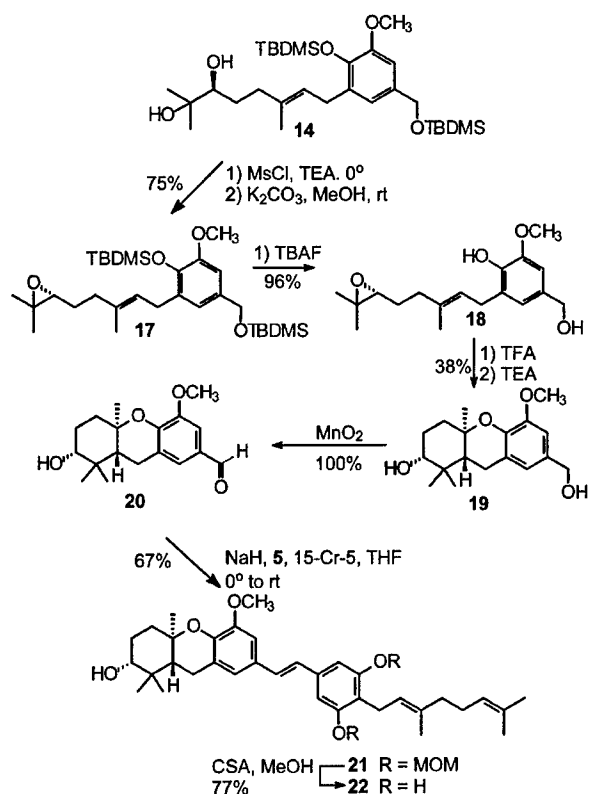


FIGURE 4. Mosher–Trost analysis of *O*-methylmandelate esters.

SCHEME 4



Treatment of diol **14** with mesyl chloride and base, followed by in situ nucleophilic displacement of the resulting mesylate by the tertiary alkoxide, did in fact deliver the nonracemic epoxide **17** in good yield (Scheme 4). Deprotection of epoxide **17** to the diol **18** followed by treatment with trifluoroacetic acid to induce cyclization gave the expected tricycle as the trifluoroacetate ester, and subsequent hydrolysis gave the benzyl alcohol of compound **19** is indeed in an equatorial disposition is evidenced by the large coupling constant ($J_{(\text{H}_{2\text{ax}}-\text{H}_{3\text{ax}})} = 11.9 \text{ Hz}$) observed in the ^1H NMR spectrum. Manganese dioxide oxidation cleanly affords aldehyde **20**, and condensation with phosphonate **5** under modified Horner–

Wadsworth–Emmons conditions¹⁷ gave the protected stilbene **21** in high yield, all without recourse to protection of the secondary alcohol. Final deprotection of the MOM ethers upon treatment with camphorsulfonic acid gave enantioenriched 3-deoxyschweinfurthin B (**22**) in good yield.¹⁸

After the viability of this strategy had been demonstrated with enantioenriched epoxide **17**, application of this approach to enantiopure material was pursued. The initial studies with a phenyl selenide cyclization precursor had been made with the assumption that this large substituent could ultimately be used to transfer absolute stereocontrol through a cationic cyclization manifold. There was some reason, however, to question this hypothesis. It had been noted in reactions of episulfonium ions that there is potential for the positive charge to be carried by either center of the three-membered ring intermediate.¹⁹ In contrast there is literature precedent for faithful transmission of stereochemical information through the epoxide cyclization transition state,²⁰ but to determine the stereointegrity of this specific case, a resolution of the enantioenriched material was required. Our experience with the Trost–Mosher esters **15** and **16** indicated this should be straightforward. To this end a large-scale esterification was conducted (Scheme 5), and the resulting material was readily partitioned into major (**15**) and minor diastereomers by flash chromatography. Hydrolysis of the major ester **15** was accomplished upon treatment with sodium hydroxide in ethanol to afford diol (*S*)-**14** as a single enantiomer.²¹

The diol (*S*)-**14** then was subjected to the same protocols developed for the epoxide cyclization which led to tricyclic material in the enantioenriched series. Treatment with mesyl chloride followed by internal displacement mediated by potassium carbonate gave the epoxide (*R*)-**17** in moderate yield. Removal of the silyl ether protecting groups and subsequent cyclization with trifluoroacetic acid gave, as expected, the tricyclic diol (*R,R,R*)-**19** in reasonable yield. This diol could be subjected to benzylic oxidation with manganese dioxide to afford the aldehyde (*R,R,R*)-**20**.

The aldehyde (*R,R,R*)-**20** displayed a specific rotation of $+159^\circ$. Two other samples of optically active compound **20** also were available: one with a rotation of $+97.8^\circ$ for material synthesized from diol **14** with an enantiomeric excess of 64% ($[\alpha]_D = -6.1^\circ$), and another with a rotation of $+112^\circ$ from diol **14** with an enantiomeric excess of 74% ($[\alpha]_D = -7.0^\circ$). On the basis of the rotation of the enantiopure aldehyde (*R,R,R*)-**20**, these values would correspond to ee's of 63% and 72%, respectively, indicating that this cascade cyclization is stereospecific within

(17) Baker, R.; Sims, R. J. *Synthesis* **1981**, 117.

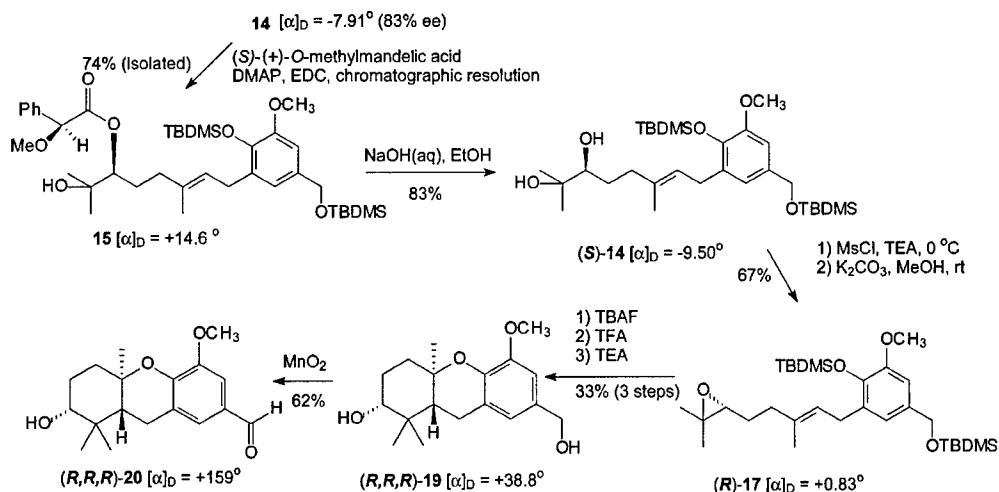
(18) Iikubo, K.; Ishikawa, Y.; Ando, N.; Umezawa, K.; Nishiyama, S. *Tetrahedron Lett.* **2002**, 43, 291–293.

(19) (a) Branchaud, B. P.; Blanchette, H. S. *Tetrahedron Lett.* **2002**, 43, 351–353. (b) Toshimitsu, A.; Hirosawa, C.; Tamao, K. *Synlett* **1996**, 465–467.

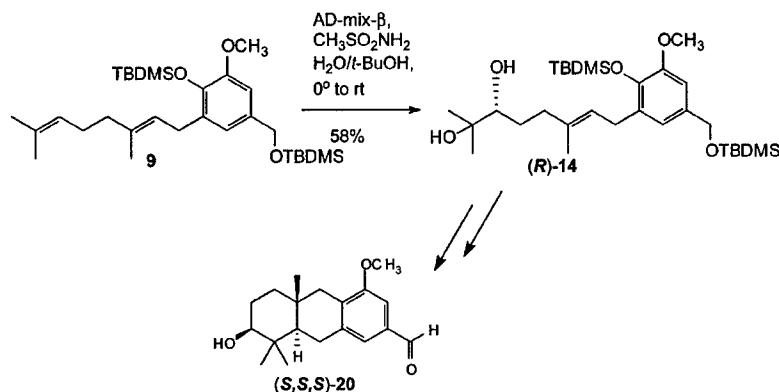
(20) (a) Corey, E. J.; Lee, J. J. *Am. Chem. Soc.* **1993**, 115, 8873–8874. (b) Corey, E. J.; Lin, S. J. *Am. Chem. Soc.* **1996**, 118, 8765–8766. (c) Corey, E. J.; Lou, G.; Lin, S. J. *Am. Chem. Soc.* **1997**, 119, 9927–9928. (d) Corey, E. J.; Lou, G.; Lin, L. S. *Angew. Chem., Int. Ed.* **1998**, 37, 1126–1128. (e) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, 121, 9999–10003. (f) Zhang, J.; Corey, E. J. *Org. Lett.* **2001**, 3, 3215–3216 and references therein.

(21) Schneider, J. P.; Kelly, J. W. *J. Am. Chem. Soc.* **1995**, 117, 2533–2546.

SCHEME 5

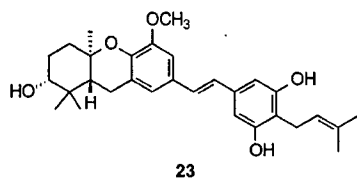


SCHEME 6



the error of these measurements. It should be noted that oxidation of compound **9** with the AD-mix- β reagent affords the diol (*R*)-**14** in similar yield and enantiopurity (Scheme 6). The tricyclic aldehyde (*S,S,S*)-**20** has been synthesized from diol (*R*)-**14** via this route as well, thus providing access to either enantiomer of compound **22**.

Enantioenriched compound **22** was tested at the NCI in the 60 cell line anticancer assay, and was found to have a mean GI₅₀ of 0.21 μ M, slightly lower than those of any of the natural schweinfurthins. The finding of more potent activity in this analogue is significant and makes this compound an interesting addition to a family which warrants further study. Furthermore, the viability of the epoxide cyclization suggests that the biosynthesis of the natural schweinfurthins may follow a similar reaction manifold. In that context, the very recent report of the natural product **23**,²² identical to 3-deoxyschweinfurthin B except for the D-ring prenyl substituent that replaces the geranyl group of schweinfurthin B, is intriguing and strongly suggests that 3-deoxyschweinfurthin B may someday be found as a natural product.



In conclusion, a cascade cyclization of an epoxy olefin has been used to prepare the carbon skeleton of the hexahydroxanthene unit found in schweinfurthins A, B, and D. Furthermore, an aldehyde derived from this tricyclic compound has been condensed with the right-half synthon reported earlier to afford the complete schweinfurthin skeleton in a product that can be viewed as 3-deoxyschweinfurthin B. This work represents the first synthesis of a tetracyclic schweinfurthin analogue and, with absolute stereochemistry derived from an AD-mix reagent, can afford the final product as a single enantiomer. These efforts validate the strategies we have developed for the synthesis of this family of natural products. Application of these strategies to preparation of the natural compounds, as well as the results of bioassays conducted on various synthetic materials, will be reported in due course.

Experimental Section

Olefin 13. To a solution of the alcohol **7** (32 mg, 0.07 mmol) in THF (5 mL) at -10 °C was added *m*-CPBA (24 mg, 0.1 mmol, 70% technical grade). The resulting solution was stirred for 40 min and transferred into a solution of diisopropylamine

(22) Yoder, B. J.; Schilling, J. K.; Norris, A.; Miller, J. S.; Andrian-tsiferana, R.; Rasamison, V. E.; Kingston, D. G. I. International Congress on Natural Products Research, Phoenix, AZ, August 2004; Paper O-16.

(30 μ L, 0.22 mmol) in toluene (30 mL) at reflux. After 3 h the mixture was allowed to cool to rt and quenched by addition of 10% aqueous sodium sulfite. The mixture was extracted with EtOAc, and the organic phase was washed with brine, dried (MgSO_4), and then concentrated in vacuo. The resulting yellow oil was subjected to final purification by column chromatography (10:1, 4:1, and 3:2 hexanes/ethyl acetate) to afford the olefin **13** (13 mg, 62%) as a clear oil: ^1H NMR δ 6.75 (s, 1H), 6.71 (s, 1H), 5.55 (dt, J = 10.3, 4.0 Hz, 1H), 5.42 (dt, J = 10.1, 1.9 Hz, 1H), 4.59 (s, 2H), 3.86 (s, 3H), 2.74 (m, 2H), 2.46 (dd, J = 11.9, 6.15 Hz, 1H), 2.01 (dd, J = 3.9, 1.9 Hz, 2H), 1.28 (s, 3H), 1.10 (s, 3H), 0.99 (s, 3H); ^{13}C NMR δ 148.6, 142.2, 137.7, 131.7, 122.5, 120.6, 120.3, 108.6, 76.6, 65.6, 56.1, 44.5, 39.5, 35.9, 31.3, 23.3, 23.1, 20.1; HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{24}\text{O}_3$ 288.1725, found 288.1727.

3-(3',7'-Dimethyl-2-octen-6'(S),7'-diol)-4-(tert-butyldimethylsiloxy)-5-methoxybenzyloxy]-tert-butyldimethylsilane (14). To a solution of AD-mix- α (15.13 g) in water/*t*-BuOH (150 mL, 1:1) was added methanesulfonamide (1.13 g), and the solution was cooled to 6 $^\circ\text{C}$. The geranylated arene **9**⁴ (5.29 g, 10.2 mmol) was added via syringe as a neat oil, and the solution was kept at 6 $^\circ\text{C}$ for 15 h. Solid Na_2SO_3 was added, and the solution was stirred for 1 h. The solution was extracted with EtOAc, and the resulting organic layer was washed with 2 N NaOH and brine, then dried (MgSO_4), and concentrated in vacuo to afford a clear oil. Final purification by column chromatography (1:1 hexanes/ethyl acetate) gave the diol **14** (3.86 g, 68%) as a clear oil: $[\alpha]_{\text{D}}^{26.4} = -7.9$ (c 0.10, CHCl_3); ^1H NMR δ 6.72 (d, J = 2.0 Hz, 1H), 6.65 (d, J = 2.0 Hz, 1H), 5.38 (t, J = 7.1 Hz, 1H), 4.64 (s, 2H), 3.77 (s, 3H), 3.35 (d, J = 7.3 Hz, 2H), 3.35 (m, 1H), 2.33–2.23 (m, 2H), 2.17–2.00 (m, 2H), 1.70 (s, 3H), 1.66–1.56 (m, 1H), 1.50–1.36 (m, 1H), 1.19 (s, 3H), 1.15 (s, 3H), 1.00 (s, 9H), 0.93 (s, 9H), 0.17 (s, 6H), 0.08 (s, 6H); ^{13}C NMR δ 149.7, 141.3, 135.7, 133.7, 132.1, 123.3, 119.0, 107.3, 78.2, 73.0, 65.0, 54.7, 36.7, 29.7, 28.5, 26.4, 26.1 (3C), 25.9 (3C), 23.2, 21.0, 18.9, 16.2, –3.9 (2C), –5.2 (2C). Anal. Calcd for $\text{C}_{30}\text{H}_{56}\text{O}_5\text{Si}_2$: C, 65.17; H, 10.21. Found: C, 65.11, H, 10.22.

(S)-O-Methylmandelate 15. To a solution of diol **14** (3.65 g, 6.60 mmol), EDC (1.64 g, 8.60 mmol), and DMAP (0.83 g, 6.76 mmol) in CH_2Cl_2 (25 mL) was added (S)-(+)-O-methylmandelic acid (1.15 g, 6.93 mmol). After 1 h at rt, water was added and the resulting solution was extracted with CH_2Cl_2 . The combined organic phase was dried (MgSO_4) and concentrated. Further purification by flash chromatography (4:1 to 3:1 hexanes/ethyl acetate) afforded the mandelate ester **15** (3.77 g, 82%) as a clear oil, along with a small amount of the diastereomeric ester (not isolated): $[\alpha]_{\text{D}}^{26.4} = +14.6$ (c 0.10, CHCl_3); ^1H NMR (CDCl_3) δ 7.46 (dd, J = 7.9, 1.8 Hz, 2H), 7.40–7.32 (m, 3H), 6.72 (s, 1H), 6.64 (s, 1H), 5.27 (t, J = 8.0 Hz, 1H), 4.79 (s, 1H), 4.65 (s, 2H), 3.77 (s, 3H), 3.43 (s, 3H), 3.33 (d, J = 7.9 Hz, 2H), 1.96 (t, J = 8.0 Hz, 2H), 1.78–1.61 (m, 3H), 1.64 (s, 3H), 1.00 (s, 9H), 0.94 (s, 15H), 0.18 (s, 6H), 0.09 (s, 6H); ^{13}C NMR δ 170.4, 149.7, 141.3, 136.5, 135.0, 133.7, 132.1, 129.0, 128.7 (2C), 127.2 (2C), 123.1, 119.0, 107.3, 82.6, 80.7, 72.3, 65.0, 57.3, 54.7, 35.0, 28.5, 28.1, 26.1 (3C), 26.0 (3C), 25.9, 24.6, 18.9, 18.4, 16.3, –3.9 (2C), –5.1 (2C); HRMS (ESI) m/z calcd for $\text{C}_{39}\text{H}_{64}\text{O}_7\text{Si}_2\text{Na}$ ($\text{M} + \text{Na}$)⁺ 723.4088, found 723.4090.

(R)-O-Methylmandelate 16. In a manner identical to that described above for the preparation of ester **15**, the diol **14** (38 mg, 0.07 mmol), EDC (20 mg, 0.1 mmol), and DMAP (10 mg, 0.08 mmol) were allowed to react with (R)-(–)-O-methylmandelic acid (12 mg, 0.07 mmol). Standard workup and final purification by column chromatography (5:1 hexanes/ethyl acetate) afforded the target ester **16** (41.5 mg, 82%) as a clear oil along with the (R,R)-diastereomer (total yield of 100%). A diastereomeric ratio of 84:16, corresponding to an initial ee of 68% for compound **14**, was determined by integration of signals at 5.00 and 5.27 ppm in the ^1H NMR spectrum of the initial mixture. Data for diastereomer **16**: ^1H NMR δ 7.46 (d, J = 8.7 Hz, 2H), 7.36–7.28 (m, 3H), 6.73 (s, 1H), 6.57 (s, 1H), 5.00

(t, J = 6.6 Hz, 1H), 4.80 (m, 2H), 4.65 (s, 2H), 3.78 (s, 3H), 3.43 (s, 3H), 3.24 (d, J = 6.9 Hz, 2H), 1.60 (m, 5H, 1H exchanges with D_2O), 1.45 (s, 3H), 1.16 (s, 6H), 0.99 (s, 9H), 0.93 (s, 9H), 0.17 (s, 6H), 0.09 (s, 6H); ^{13}C NMR δ 170.9, 149.7, 141.3, 136.3, 134.9, 133.6, 132.1, 128.8, 128.6 (2C), 127.1 (2C), 123.0, 119.0, 107.3, 82.7, 80.7, 72.4, 65.1, 57.3, 54.7, 35.4, 28.3, 28.2, 26.6, 26.1 (3C), 26.0 (3C), 24.7, 18.9, 18.4, 16.1, –3.9 (2C), –5.1 (2C); HRFABMS m/z calcd for $\text{C}_{39}\text{H}_{64}\text{O}_7\text{NaSi}_2$ ($\text{M} + \text{Na}$)⁺ 723.4088, found 723.4101.

[4-(tert-Butyldimethylsilyloxy)-5-methoxy-3-(3',7'-dimethyl-6'-epoxy-2'-octenyl)benzyloxy]-tert-butyldimethylsilane (17). To a solution of diol **14** (2.03 g, 3.7 mmol), in CH_2Cl_2 (20 mL) at 0 $^\circ\text{C}$, was added TEA (1.35 mL, 9.69 mmol) followed 30 min later by MsCl (0.43 mL, 5.58 mmol). After 35 min, the reaction was allowed to warm to rt, and after a total of 2 h, a second aliquot of TEA (0.80 mL, 5.74 mmol) was added and the reaction was stirred for 30 min. A solution of K_2CO_3 (2.31 g, 16.7 mmol) in MeOH (70 mL) was poured into the vessel, and the solution was allowed to react for 20 h. After filtration and extraction of the resulting filtrate with ethyl acetate, the combined organic phase was washed with brine, dried (MgSO_4), and concentrated under vacuum to afford a white oil. Final purification by flash chromatography (12:1 hexanes/ethyl acetate) yielded the target epoxide **17** as a viscous clear oil (1.48 g, 75%): ^1H NMR δ 6.72 (d, J = 1.7 Hz, 1H), 6.65 (d, J = 1.6 Hz, 1H), 5.36 (tm, J = 7.2 Hz, 1H), 4.64 (s, 2H), 3.77 (s, 3H), 3.34 (d, J = 7.1 Hz, 2H), 2.72 (t, J = 6.3 Hz, 1H), 2.30–2.10 (m, 2H), 1.70 (s, 3H), 1.75–1.60 (m, 2H), 1.28 (s, 3H), 1.25 (s, 3H), 0.99 (s, 9H), 0.93 (s, 9H), 0.17 (s, 6H), 0.08 (s, 6H); ^{13}C NMR δ 149.7, 141.3, 135.0, 133.7, 132.1, 123.3, 119.0, 107.3, 65.0, 64.2, 58.3, 54.7, 36.3, 28.5, 27.4, 26.1 (3C), 26.0 (3C), 24.9, 18.9, 18.7, 18.4, 16.2, –3.9 (2C), –5.2 (2C). Anal. Calcd for $\text{C}_{30}\text{H}_{54}\text{O}_4\text{Si}_2$: C, 67.36; H, 10.17. Found: C, 67.12; H, 10.28.

(6'R)-4-Hydroxy-3-methoxy-5-(3',7'-dimethyl-6'-epoxy-2'-octenyl)benzyl Alcohol (18). Silyl ether **17** (840 mg, 1.57 mmol) was dissolved in THF (70 mL), and the solution was cooled to 0 $^\circ\text{C}$. To this solution was added TBAF (4.6 mL, 1.00 M in THF), and the reaction was allowed to warm to rt and after 1.5 h was quenched with satd NH_4Cl . After extraction with ethyl acetate, the combined organic extract was washed with water and brine, dried over MgSO_4 , and concentrated in vacuo to give a yellow oil. Final purification by flash chromatography (4:1 hexanes/ethyl acetate) gave the diol **18** (352 mg, 96%): ^1H NMR (CDCl_3) δ 6.77 (s, 1H), 6.74 (s, 1H), 5.70 (s, 1H), 5.37 (t, J = 7.3 Hz, 1H), 4.57 (d, J = 5.5 Hz, 2H), 3.89 (s, 3H), 3.36 (d, J = 7.3 Hz, 2H), 2.71 (t, J = 6.2 Hz, 1H), 2.24–2.12 (m, 2H), 1.74 (s, 3H), 1.68–1.62 (m, 3H), 1.27 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (CDCl_3) δ 146.3, 142.8, 135.3, 132.1, 127.0, 122.7, 120.7, 107.5, 65.6, 64.3, 58.4, 56.0, 36.4, 27.8, 27.3, 24.8, 18.7, 16.1. Anal. Calcd for $\text{C}_{18}\text{H}_{26}\text{O}_4 \cdot 0.5\text{H}_2\text{O}$: C, 68.55; H, 8.63. Found: C, 68.23; H, 8.53.

Diol 19. To a solution of epoxyphenol **18** (352 mg, 1.2 mmol) in CH_2Cl_2 (40 mL) at 0 $^\circ\text{C}$ was added trifluoroacetic acid (0.26 mL, 3.4 mmol). The resulting solution was allowed to stir for 2 h, and Et_3N (1.4 mL, 10.0 mmol) was added. After an additional 30 min, water (75 mL) was added, the phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with water and brine, then dried (MgSO_4), and concentrated. Final purification by flash chromatography (2:1 to 1:1 hexanes/ethyl acetate) afforded the tricyclic diol **19** (135 mg, 38%) as a light yellow oil: ^1H NMR (CDCl_3) δ 6.73 (s, 1H), 6.70 (s, 1H), 4.57 (s, 2H), 3.86 (s, 3H), 3.39 (dd, J = 11.6, 3.8 Hz, 1H), 2.69 (d, J = 8.9 Hz, 2H), 2.15–2.04 (m, 2H), 1.88–1.59 (m, 6H, 2H exchange with D_2O), 1.23 (s, 3H), 1.08 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (CDCl_3) δ 148.9, 142.1, 132.0, 122.5, 120.4, 108.5, 78.0, 76.8, 65.5, 56.0, 46.7, 38.3, 37.6, 28.3, 27.3, 23.1, 19.7, 14.2; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{26}\text{O}_4$ (M^+) 306.1831, found 306.1823.

Aldehyde 20. To a solution of benzylic alcohol **19** (251 mg, 0.82 mmol) in CH_2Cl_2 (30 mL) was added MnO_2 (1.71 g, 19.6

mmol) as a single aliquot. The resulting suspension was allowed to stir for 26 h and then filtered through Celite, and the residue was concentrated in vacuo to afford the aldehyde **20** as a white solid (249 mg, 100%): mp 160.5–162.0 °C; $[\alpha]_D^{25.0} = +97.8$ (c 0.126, CHCl₃); ¹H NMR (CDCl₃) δ 9.80 (s, 1H), 7.25 (s, 1H), 7.24 (s, 1H), 3.90 (s, 3H), 3.45 (dd, *J* = 11.4, 3.8 Hz, 1H), 2.80–2.77 (m, 2H), 2.22–2.15 (m, 1H), 1.94–1.82 (m, 2H), 1.74–1.61 (m, 2H), 1.28 (s, 3H), 1.13 (s, 3H), 0.91 (s, 3H); ¹³C NMR δ 191.1, 149.5, 148.7, 128.7, 127.3, 122.5, 107.3, 78.4, 77.8, 56.0, 46.5, 38.4, 37.5, 28.2, 27.3, 23.0, 20.0, 14.3. HRMS *m/z* calcd for C₁₈H₂₅O₄ (M + H)⁺ 305.1753, found 305.1743. Anal. Calcd for C₁₈H₂₄O₄·H₂O: C, 67.06; H, 8.13. Found: C, 66.98; H, 8.17.

3-Deoxydimethoxymethylschweinfurthin B (21). A suspension of NaH (29 mg, 1.2 mmol) and 15-crown-5 (4 μL, 0.02 mmol) in THF (1.5 mL) was cooled to 5 °C. To this were added aldehyde **20** (10 mg, 0.03 mmol) and phosphonate **5** (22 mg, 0.05 mmol) in THF (2 mL). The mixture was allowed to warm to rt and stirred for a total of 18 h. Water was added dropwise, and the solution was extracted with ether. The resulting organic phase was washed with brine, dried over MgSO₄, and concentrated in vacuo. Final purification by column chromatography (3.5:1 to 1:1 hexanes/ethyl acetate) gave the stilbene **21** (15.2 mg, 80%) as a straw-colored oil: ¹H NMR (CDCl₃) δ 6.95–6.85 (m, 6H), 5.24 (s, 4H), 5.24 (t, 1H), 5.07 (t, *J* = 11.7 Hz, 1H), 3.89 (s, 3H), 3.50 (s, 6H), 3.40 (m, 3H), 2.72 (d, *J* = 8.7 Hz, 2H), 2.16–1.85 (m, 7H), 1.79 (s, 3H), 1.70–1.65 (m, 3H), 1.65 (s, 3H), 1.57 (s, 3H), 1.26 (s, 3H), 1.10 (s, 3H), 0.89 (s, 3H); ¹³C NMR (CDCl₃) δ 155.9 (2C), 148.9, 142.5, 136.7, 134.6, 131.2, 128.9, 128.2, 126.4, 124.3, 122.6, 122.5, 120.5, 119.5, 106.8, 105.9 (2C), 94.5 (2C), 78.1, 77.0, 55.9 (2C), 55.9, 46.7, 39.8, 38.4, 37.7, 28.3, 27.3, 26.7, 25.6, 23.1, 22.7, 19.8, 17.6, 16.0, 14.3; HRMS (ESI) *m/z* calcd for C₃₉H₅₄O₇ (M⁺) 634.3870, found 634.3871.

3-Deoxyschweinfurthin B (22). To a solution of stilbene **21** (24 mg, 0.04 mmol) in MeOH (2 mL) was added camphor-sulfonic acid (10 mg, 0.04 mmol). The resulting solution was stirred at rt for 20 h and then heated to 60 °C for an additional 5 h. The reaction was quenched by addition of satd NaHCO₃ and extracted with ethyl acetate, and the organic phase was washed with brine and dried over MgSO₄. Concentration in vacuo, followed by final purification by column chromatography (1:1 hexanes/ethyl acetate), afforded **22** (16 mg, 79%) as a clear oil: ¹H NMR (CDCl₃) δ 6.83 (m, 4H), 6.55 (s, 2H), 5.31 (s, 1H), 5.28 (t, *J* = 6.9 Hz, 1H), 5.06 (m, 1H), 3.88 (s, 3H), 3.43 (m, 3H), 2.72 (d, *J* = 9.1 Hz, 2H), 2.15–2.06 (m, 5H), 1.90–1.82 (m, 3H), 1.82 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.25 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H); ¹³C NMR (CDCl₃) δ 155.2 (2C), 148.9, 142.7, 139.2, 137.1, 132.1, 128.8, 128.6, 125.7, 124.2, 122.6, 121.4, 120.6, 112.8, 107.0, 106.2 (2C), 78.0, 77.1, 55.0, 46.8, 39.7, 38.4, 37.6, 28.3, 27.3, 26.4, 25.7, 23.1, 22.5, 19.8, 17.7, 16.2, 14.3; HRMS (ESI) *m/z* calcd for C₃₅H₄₆O₅ (M⁺) 546.3345, found 546.3342.

(-)-3-(3',7'-Dimethyl-2-octen-6'(S),7'-diol)-4-(tert-butyl-dimethylsiloxy)-5-methoxybenzyloxy-tert-butyl-dimethylsilane ((S)-14). To a solution of mandelate ester **15** (203 mg, 0.29 mmol) in EtOH (10 mL) was added NaOH (0.63 mL, 0.63 mmol, aq, 1 M). After 5 h at rt, HCl (0.63 mL, 0.063 mmol, aq, 1 M) was added and the mixture was extracted with ethyl acetate. The combined organic phase was washed with water and brine, then dried (MgSO₄), and concentrated in vacuo to give a slightly yellow oil. Purification by column chromatography (1:1 hexanes/EtOAc) afforded the diol (S)-**14** (132 mg, 83%) as a colorless oil: $[\alpha]_D^{25.0} = -9.6$ (c 0.03, CHCl₃); spectral data were identical to those of the enantioenriched diol **14**.

(+)-[4-(tert-Butyldimethylsiloxy)-5-methoxy-3-(3',7'-dimethyl-6(R')-epoxy-2'-octenyl)benzyloxy-tert-butyl-dimethylsilane ((R)-17)]. To a solution of diol (S)-**14** (1.41 g, 2.56 mmol), in CH₂Cl₂ (20 mL) at 0 °C, was added TEA (1.05 mL, 7.64 mmol) followed 50 min later by MsCl (0.27 mL, 3.50 mmol). After 45 min, the reaction was

allowed to warm to rt, a second aliquot of TEA (0.60 mL, 4.36 mmol) was added, and the reaction was stirred for 4 h. This solution was transferred via cannula into a suspension of K₂CO₃ (2.35 g, 17.0 mmol) in MeOH (40 mL), and the resulting suspension was allowed to react for 20 h. After filtration and extraction of the resulting filtrate with ethyl acetate, the combined organic phase was washed with brine, dried (MgSO₄), and concentrated under vacuum to afford a colorless oil. Final purification by flash chromatography (12:1 hexanes/EtOAc) yielded the target epoxide (R)-**17** as a single enantiomer (0.91 g, 67%) as a viscous colorless oil: $[\alpha]_D^{25.0} = +0.83$ (c 0.18, CHCl₃); both ¹H and ¹³C spectra were identical to those of racemate **10** and enantioenriched compound **17**.

Tricyclic Diol (R,R,R)-19. Silyl ether (R)-**17** (936 mg, 1.75 mmol) was dissolved in THF (15 mL), and the solution was cooled to 0 °C. To this solution was added TBAF (5.4 mL, 1.0 M in THF), and the reaction was allowed to warm to rt and after 2.5 h was quenched with satd NH₄Cl. After extraction with ethyl acetate, the combined organic extract was washed with brine, dried (MgSO₄), and concentrated in vacuo to give a yellow oil. This oil (430 mg, 1.4 mmol) was dissolved in CH₂Cl₂ (60 mL) at 0 °C, and trifluoroacetic acid (0.3 mL, 3.89 mmol) was added. The resulting solution was allowed to stir 5 h, and then Et₃N (0.7 mL, 5.09 mmol) was added. After an additional 1 h, water (20 mL) was added, the phases were separated, and the aqueous phase was extracted with CHCl₃. The combined organic phase was washed with brine, then dried (MgSO₄), and concentrated. Final purification by flash chromatography (2:1 to 1:1 hexanes/EtOAc) afforded the tricyclic diol (R,R,R)-**19** (177 mg, 33% from epoxide (R)-**17**) as a light yellow oil: $[\alpha]_D^{25.0} = +38.8$ (c 0.03, CHCl₃); spectral data were identical to those of the enantioenriched diol **19**.

Aldehyde (R,R,R)-20. To a solution of benzylic alcohol (R,R,R)-**19** (118 mg, 0.4 mmol) in CH₂Cl₂ (15 mL) was added MnO₂ (954 mg, 11.0 mmol) as a single aliquot. The resulting suspension was allowed to stir for 19 h and then filtered through Celite, and the residue was concentrated in vacuo to give a yellow solid. Final purification by flash chromatography (3:1 hexane/EtOAc) gave the aldehyde (R,R,R)-**20** as a white solid (74 mg, 62%): $[\alpha]_D^{25.0} = +159$ (c 0.012, CHCl₃); the spectral data were identical to those of the enantioenriched aldehyde **20**.

3-(3',7'-Dimethyl-2-octen-6'(R),7'-diol)-4-(tert-butyl-dimethylsiloxy)-5-methoxybenzyloxy-tert-butyl-dimethylsilane ((R)-14). To a solution of AD-mix-β (8.57 g) in water/*t*-BuOH (100 mL, 1:1) was added methanesulfonamide (0.62 g), and the solution was cooled to 0 °C. The geranylated arene **9** (3.19 g, 6.15 mmol) was added via syringe as a neat oil, and the solution was kept at 0 °C for 20 h. Solid Na₂SO₃ was added, and the solution was stirred for 1 h. The solution was extracted with EtOAc, and the resulting organic layer was washed with 2 N NaOH and brine, then dried (MgSO₄), and concentrated in vacuo to afford a clear oil. Final purification by column chromatography (1:1 hexanes/EtOAc) gave the diol (R)-**14** (1.97 g, 58%) as a clear oil: $[\alpha]_D^{25.0} = +8.5$ (86% ee) (c 0.223, CHCl₃); both ¹H and ¹³C NMR spectra were identical to those of diol (S)-**14**.

Acknowledgment. Financial support from the Breast Cancer Research Program (Grants DAMD17-01-1-0276 and DAMD17-02-1-0423) and the University of Iowa Graduate College is gratefully acknowledged.

Supporting Information Available: General experimental procedures and ¹H and ¹³C NMR spectra for compounds **13**, **15**, **16**, and **18–22** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO048444R

Total synthesis of pawhuskin C: a directed *ortho* metalation approach

Jeffrey D. Neighbors, Maya S. Salnikova and David F. Wiemer*

Department of Chemistry, University of Iowa, Iowa City, IA 52242-1294, USA

Received 30 November 2004; revised 17 December 2004; accepted 21 December 2004

Available online 12 January 2005

Abstract—The total synthesis of the opioid modulator pawhuskin C has been accomplished in eight steps from methyl 3,5-dihydroxybenzoate. The key step in this sequence is a directed *ortho* metalation reaction conducted without protection of a benzylic alcohol and thus presumed to involve a formal dianion intermediate.
© 2005 Elsevier Ltd. All rights reserved.

Earlier this year, Belofsky et al. reported isolation of a small set of natural opioid receptor modulators named pawhuskin A–C (1–3, Fig. 1) from *Dalea purpurea*,¹ a plant once used by Plains Indians in North America. These compounds are prenylated stilbenes and as such display structural similarity to the schweinfurthins, a family of natural products with anticancer activity.² In-

deed pawhuskin C (3) includes a geranylated resorcinol also found in three of the natural schweinfurthins as well as the synthetic analogue 3-deoxyschweinfurthin B (4, Fig. 2).³ As an initial step toward the pawhuskin family of natural products, the phosphonate 5 was identified as a synthon for the right half of compound 3. A first generation synthesis of phosphonate 5 was disclosed in connection with the total synthesis of schweinfurthin C,⁴ and allowed use of a late stage Horner–Wadworth–Emmons (HWE) condensation to establish the central

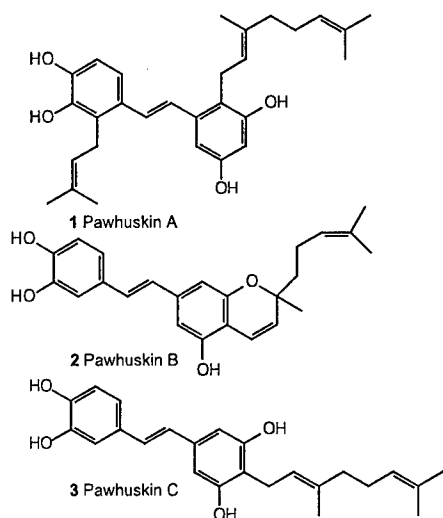


Figure 1. The pawhuskins.

Keywords: Pawhuskin; Directed *ortho* metalation.

* Corresponding author. Tel.: +1 319 335 1365; fax: +1 319 335 1270; e-mail: david-wiemer@uiowa.edu

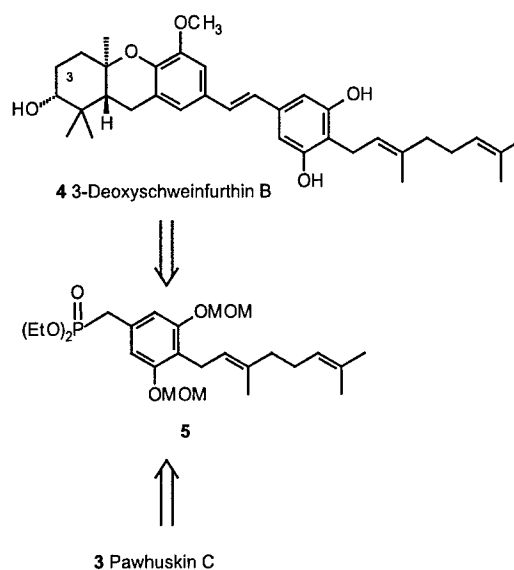


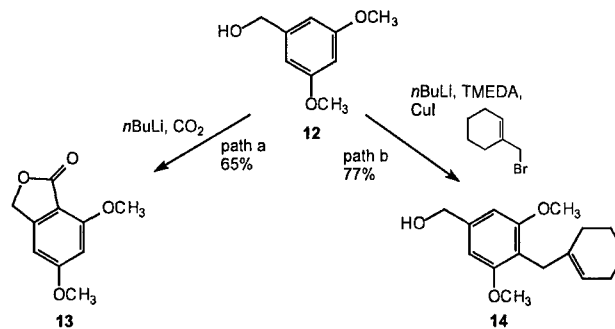
Figure 2. Retrosynthetic analysis.

stilbene olefin. While a similar strategy might be used to prepare pawhuskin C, a more efficient synthesis of the phosphonate intermediate **5** would make this route more attractive.

The initial route to phosphonate **5** (Scheme 1) commenced with the commercial resorcinol **6**. The resorcinol hydroxyl groups were protected as methoxymethyl (MOM) ethers followed by reduction of the ester to give benzylic alcohol **7**. Protection of the benzylic alcohol as a silyl ether gave arene **8**. This compound was subjected to directed *ortho* metalation (DoM) conditions followed by lithium–copper exchange and alkylation to install the geranyl chain and set the entire carbon skeleton for the right half of pawhuskin C in silyl ether **9**. Removal of the silyl ether and functional group manipulation at the benzylic position afforded the required phosphonate **5** in eight steps and 34% overall yield from ester **6**.

This series of reactions gives access to the desired reagent **5**, but a more efficient synthesis would be attractive.⁵ Studies by several groups⁶ suggested that this route could be improved through use of DoM methodology to generate a formal dianion. Specifically, if the bis-MOM ether **7** could be regioselectively metalated at the C-4 position without introduction of the silyl ether protecting group, both the silylation and the later deprotection could be avoided. There is some literature precedent, which suggested that a selective DoM reaction could be accomplished. Treatment of the dimethoxy compound **12** with *n*BuLi in hexanes affords the product of metalation at the C-2 position, compound **13** (Scheme 2, path a),⁷ whereas use of *n*BuLi with TMEDA and lithium–copper exchange gives the product where metalation has been directed to the C-4 position **14** (path b).⁸

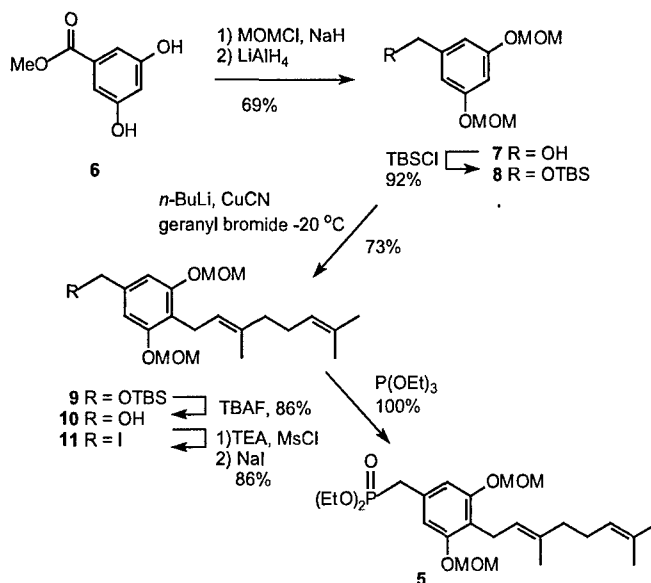
It might be possible to alkylate the dimethoxy compound **12** with geranyl bromide, and subsequently cleave the methyl ethers to phenols. However, we chose



Scheme 2.

instead to explore alkylation of the protected resorcinol **7** because the MOM ethers would be easier to remove. After some experimentation (Table 1), it was found that reaction of the MOM protected resorcinol **7** with *n*BuLi and TMEDA, followed by treatment with copper bromide–dimethyl sulfide and geranyl bromide at –20 °C, gave the alkylated benzylic alcohol **10** in yields comparable to those observed with the protected analogue **8** (Scheme 3).¹⁰ This route allows access to the phosphonate **5** in just six steps and 37% yield. This represents several improvements over the first generation route, notably in the removal of a protection/deprotection sequence. This strategy saves significant time and effort, while also allowing use of the less toxic CuBr reagent in place of the CuCN used in the first generation approach.

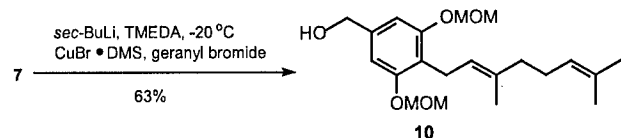
To complete the synthesis of pawhuskin C, the known benzaldehyde **15**⁹ (Scheme 4) was treated with phosphonate **5** and sodium hydride in the presence of catalytic 15-crown-5 to initiate an HWE condensation and afford the stilbene **16** in good yield.¹¹ This stilbene bearing four MOM protecting groups was subjected to acidic hydro-



Scheme 1.

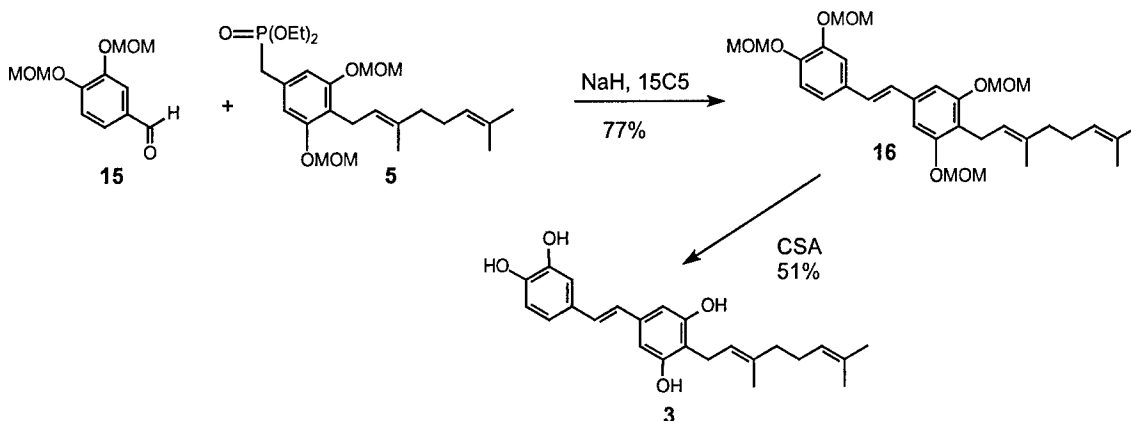
Table 1. Conditions explored for dianion DoM reaction of arene **7** and geranyl bromide (RX) in the presence of TMEDA (2 equiv)

Trial	Base, equiv, addition <i>T</i>	CuBr·DMS (equiv, <i>T</i>)	Addition <i>T</i> for RX	Yield (%)
1	<i>n</i> BuLi, 2.5 equiv, –20 °C	—	–78 °C	NR
2	<i>n</i> BuLi, 2.5 equiv, –20 °C	2.0 equiv, –20 °C	–78 °C	NR
3	KH (excess), <i>n</i> BuLi, 3.3 equiv, –78 °C	—	–78 °C	NR
4	KH (excess), <i>n</i> BuLi, 2.7 equiv, –20 °C	—	–78 °C	13
5	KH (excess), <i>n</i> BuLi, 3.0 equiv, –20 °C	—	–20 °C	17
6	KH (excess), <i>n</i> BuLi, 3.0 equiv, –20 °C	2.0 equiv, –20 °C	–20 °C	41
7	<i>n</i> BuLi, 3.3 equiv, –20 °C	2.0 equiv, –20 °C	–20 °C	57
8	<i>s</i> BuLi, 2.4 equiv, –20 °C	2.0 equiv, –20 °C	–20 °C	63

**Scheme 3.**

lysis with camphorsulfonic acid (CSA) to give the natural product pawhuskin C (**3**) in moderate yield.¹² The synthetic material was identical to the natural product in all respects including ¹H and ¹³C NMR as well as TLC comparison with an authentic sample (*R*_f = 0.10 in 2:1 hexanes/ethyl acetate).

The current studies confirm the structure of the natural product pawhuskin C through total synthesis, and expand the utility of the dianion DoM type approach in alkylation of suitably functionalized benzylic alcohols. Through elimination of two steps from the previous synthetic sequence to phosphonate **5**, this route facilitates the large scale access to this phosphonate and advances efforts directed at synthesis of other pawhuskin or schweinfurthin analogues. This phosphonate also can be used in synthetic and medicinal chemistry efforts aimed at other prenylated or geranylated stilbenes. The current effort required just eight steps to achieve the synthesis of the opioid modulator pawhuskin C in 15% overall yield, and provides an excellent example of this potential. Further work in these areas will be disclosed in due course.

**Scheme 4.**

Acknowledgements

We thank Professor Gil Belofsky (University of Tulsa) for providing an authentic sample of pawhuskin C. Financial support from the Breast Cancer Research Program (DAMD17-01-1-0276 and DAMD17-02-1-0423) and the University of Iowa Graduate College is gratefully acknowledged.

References and notes

- Belofsky, G.; French, A. N.; Wallace, D. R.; Dodson, S. L. *J. Nat. Prod.* **2004**, *67*, 26–30.
- (a) Beutler, J. A.; Schoemaker, R. H.; Johnson, T.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 1509–1512; (b) Beutler, J. A.; Jato, J.; Cragg, G. M.; Boyd, M. R. *Nat. Prod. Lett.* **2000**, *14*, 349–404.
- Neighbors, J. D.; Beutler, J. A.; Wiemer, D. F. *J. Org. Chem.* **2005**, in press.
- Treadwell, E. M.; Cermak, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718–8723.
- Trost, B. M. *Science* **1991**, *254*, 1471–1477.
- (a) Uemura, M.; Tokuyama, S.; Sakan, T. *Chem. Lett.* **1975**, 1195–1198; (b) Uemura, M.; Nishikawa, N.; Take, K.; Ohnishi, M.; Hirotsu, K.; Higuchi, T.; Hayashi, Y. *J. Org. Chem.* **1983**, *48*, 2349–2356; (c) Sinha, S.; Mandal, B.; Chandrasekaran, S. *Tetrahedron Lett.* **2000**, *41*, 3157–3160.
- Trost, B. M.; Rivers, G. T.; Gold, J. M. *J. Org. Chem.* **1980**, *45*, 1835–1838.
- Bradbury, B. J.; Bartyzel, P.; Kaufman, T. S.; Nieto, M. J.; Sindelar, R. D.; Scesney, S. M.; Gaumond, B. R.; Marsh, H. C. *J. Med. Chem.* **2003**, *46*, 2697–2705.

9. Wang, Y.; Mathis, C. A.; Haung, G.; Holt, D. P.; Debnath, M. L.; Klunk, W. E. *J. Labelled Compd. Radiopharm.* **2002**, *45*, 647–664.
10. [4-(3,7-Dimethyl-octa-2,6-dienyl)-3,5-dimethoxymethoxy-phenyl]-methanol (**10**). *sec*-BuLi (8.0 mL, 1.00 M in hexanes) was added dropwise to a solution of benzylic alcohol **7** (772 mg, 3.37 mmol) and TMEDA (1.10 mL, 7.28 mmol) in THF (20 mL) at -20°C . After this solution was stirred for 1 h at -20°C , CuBr as its DMS complex (1.39 mg, 6.76 mmol) was added in one portion and the mixture was stirred for 1 h at -20°C . Geranyl bromide (0.75 mL, 3.77 mmol) was added dropwise and the reaction mixture was stirred for 2 h at -20°C . The reaction was quenched by addition of 1 N NH_4Cl , the aqueous layer was neutralized to pH 7 with 1 N HCl, and then was extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO_4), and concentrated in vacuo. Final purification by flash column chromatography (40% EtOAc in hexanes) afforded compound **10**⁴ (773 mg, 63%) as a clear yellow oil.
11. Tetra-MOM ether **16**. A suspension of NaH (36 mg, 1.5 mmol) and 15-crown-5 (4 μL , 0.02 mmol) in THF (10 mL) was cooled to 0°C . Aldehyde **15** (32 mg, 0.14 mmol) and phosphonate **5** (94 mg, 0.19 mmol) in THF (2 mL) were added, and the mixture was allowed to warm to rt and stirred for a total of 18 h. Water was added dropwise, and the solution was extracted with EtOAc. The resulting organic phase was washed with brine, dried over MgSO_4 , and concentrated in vacuo. Final purification by column chromatography (4:1 hexanes/EtOAc) gave the stilbene **16** (60 mg, 77%) as a clear oil: ^1H NMR (CDCl_3) δ 7.33–7.32 (m, 1H), 7.15–7.08 (m, 2H), 7.03–6.88 (m, 4H), 5.28 (s, 2H), 5.24 (s, 2H), 5.23 (s, 4H), 5.22–5.19 (m, 1H), 5.11–5.04 (m, 1H), 3.56 (s, 3H), 3.53 (s, 3H), 3.50 (s, 6H), 3.40 (d, $J = 7.2$ Hz, 2H), 2.08–2.01 (m, 2H), 1.98–1.93 (m, 2H), 1.79 (s, 3H), 1.64 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (CDCl_3) δ 155.9 (2C), 147.4, 146.8, 136.4, 134.6, 132.2, 131.2, 127.7, 127.7, 124.4, 122.6, 121.0, 119.8, 116.6, 114.3, 106.1 (2C), 95.4, 95.4, 94.5 (2C), 56.2, 56.2, 56.0 (2C), 39.8, 26.7, 25.6, 22.7, 17.6, 16.1; HRMS calcd for $\text{C}_{32}\text{H}_{45}\text{O}_8$ ($\text{M}+\text{H}$)⁺ 557.3114, found 557.3130.
12. Pawhuskin C (**3**). To a solution of stilbene **16** (60 mg, 0.11 mmol) in MeOH (10 mL) was added a catalytic amount of camphorsulfonic acid, and the resulting solution was stirred at rt for 24 h. The reaction was quenched by addition of satd NaHCO_3 , extracted with ethyl acetate, and the organic phase was washed with brine and dried (MgSO_4). Concentration in vacuo, followed by final purification by column chromatography (1:1, hexanes/ethyl acetate) afforded pawhuskin C (**3**, 21 mg, 51%) as a yellow solid; all spectral characteristics matched the published data.¹

Draft: 3/25/05

Synthesis and Structure Activity Studies of Schweinfurthin B Analogs: Evidence for the Importance of a Hydrogen Bond Donor in Expression of Differential Cytotoxicity.

Jeffrey D. Neighbors,^{†¶} Maya Salnikova,[†] John A. Beutler,[‡] and David F. Wiemer^{*†¶}

Departments of Chemistry[†] and Pharmacology[¶]

University of Iowa

Iowa City, Iowa 52242-1294

National Cancer Institute[‡]

Molecular Targets Development Program

Center for Cancer Research

Frederick, Maryland 21701

* Corresponding author. Tel: 319-335-1365; Fax: 319-335-1270; e-mail: david-wiemer@uiowa.edu

Abstract: Synthesis and bioactivity of several enatioenriched schweinfurthins B analogs is described. All of the target stilbenes contain a common left half hexahydroxanthene ring system and an aromatic right half with varied substituents. The synthesis involves penultimate Horner-Wadsworth-Emmons coupling of one of several right-half phosphonates with the aldehyde comprising the left-half of 3-deoxyschweinfurthin B. We describe the synthesis of the requisite phosphonates, and the respective stilbenes, as well as the cytotoxicity profiles of these new compounds in the National Cancer Institute's 60 cell-line anticancer screen. Several of these analogs displayed differential cytotoxicity well-correlated with the natural products. Together, these assay results indicate the importance of at least one free hydroxyl group on the aromatic D-ring of this system for differential cytotoxicity.

Introduction

The schweinfurthins are a small set of natural stilbenes isolated from the African tree *Macaranga schweinfurthii* at National Cancer Institute (NCI) in the late 1990's.¹ These compounds were isolated through bioassay guided fractionation as part of the Developmental Therapeutics Program at NCI, and three of the four were found to have significant and differential cytotoxicity in the NCI's 60 cell-line anticancer screen. Schweinfurthin A (**1**) and schweinfurthin B (**2**, Figure 1) presented mean GI₅₀'s of 0.36 and 0.81 μ M respectively and schweinfurthin D (**4**) was found to be equipotent

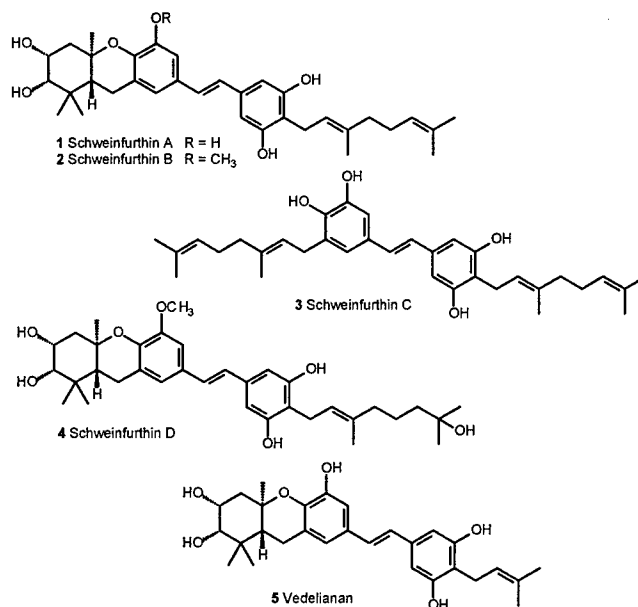


Figure 1. The schweinfurthin family and related natural products.

with schweinfurthin B (**2**).^{1b} The fourth member of this family, schweinfurthin C (**3**), lacks the left-half hexahydroanthrene core and displayed little differential activity and considerably reduced cytotoxicity in initial screens. Vedelianin (**5**), a closely related natural product, has been shown to have cytotoxic activity similar to schweinfurthin A (**1**).²

To prioritize their investigations, the NCI utilizes a bioinformatics algorithm known as COMPARE to search for correlations between patterns of cytotoxic activity in the 60 cell-line assays.³ Compounds which act on the same molecular targets typically display a higher degree of correlation across the various cell lines and sub-panels of the screen. The schweinfurthins differential activity presented with CNS, renal, leukemia, and some breast cancer cell lines showing high susceptibility, while many ovarian, melanoma, and lung cancer lines were resistant. The specific pattern was not correlated to any compound in the NCI standard agents database by COMPARE analysis and this could indicate that these cytotoxins act via a novel cellular pathway or target.⁴ Because of their intriguing bioactivity as well as our ongoing interest in chemotherapeutic chemistry⁵ and prenylated aromatics in general,⁶ we undertook an effort to explore some structure activity relationships in the schweinfurthin family.

Our synthetic strategy involves a late stage introduction of the central stilbene olefin via a Horner-Wadsworth-Emmons (HWE) olefination (Figure 2). It was envisioned that this would allow maximum convergence and facilitate introduction of changes in the right-half architecture to identify the relevant pharmacophore(s) therein. Early work on the simplest member of the family, schweinfurthin C, required synthesis of the right half phosphonate **6**⁷ which also could serve as a synthon for schweinfurthins A and B. This reduced the problem of preparation of a tetracyclic schweinfurthin to synthesis of the left half hexahydroxanthene as in aldehyde **7**.

We targeted schweinfurthin B initially to derive the C-ring, including the methoxy substituents, from vanillin (**8**). Two routes involving cationic cascade cyclization to effect the formation of the A and B rings of the tricyclic system have been explored

(Figure 3). With the substantial literature precedents for the diastereoselectivity of such processes⁸ the primary issue became one of introducing the initial stereocenter to allow substrate control through the cascade manifold and to ensure proper relative stereochemistry. The first such process employed a phenylselenide substituent (i. e. compound **9**) to direct

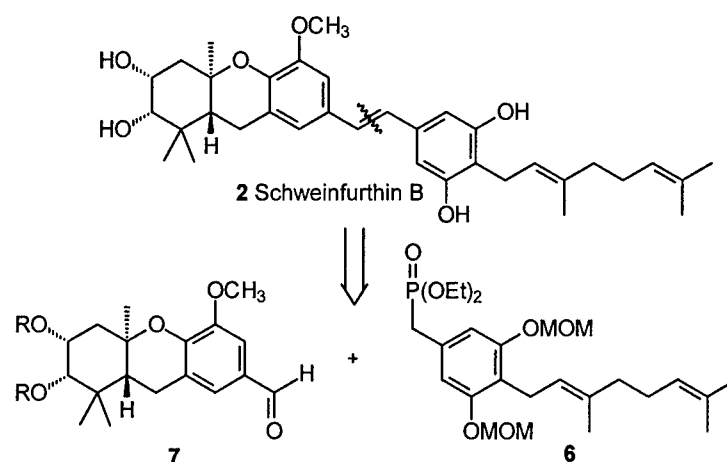


Figure 2. HWE strategy

the diastereoselective cascade, ultimately leading to tricyclic olefin **10**. After some experimentation a pathway involving a more biomimetic cyclization¹⁰ of epoxide **11** was found to afford tricyclic aldehyde **12**.¹¹ The epoxide **11** is available via an AD-mix α oxidation as an enantioenriched mixture with 68% ee, and all of the analogs synthesized here have a similar enantiopurity.

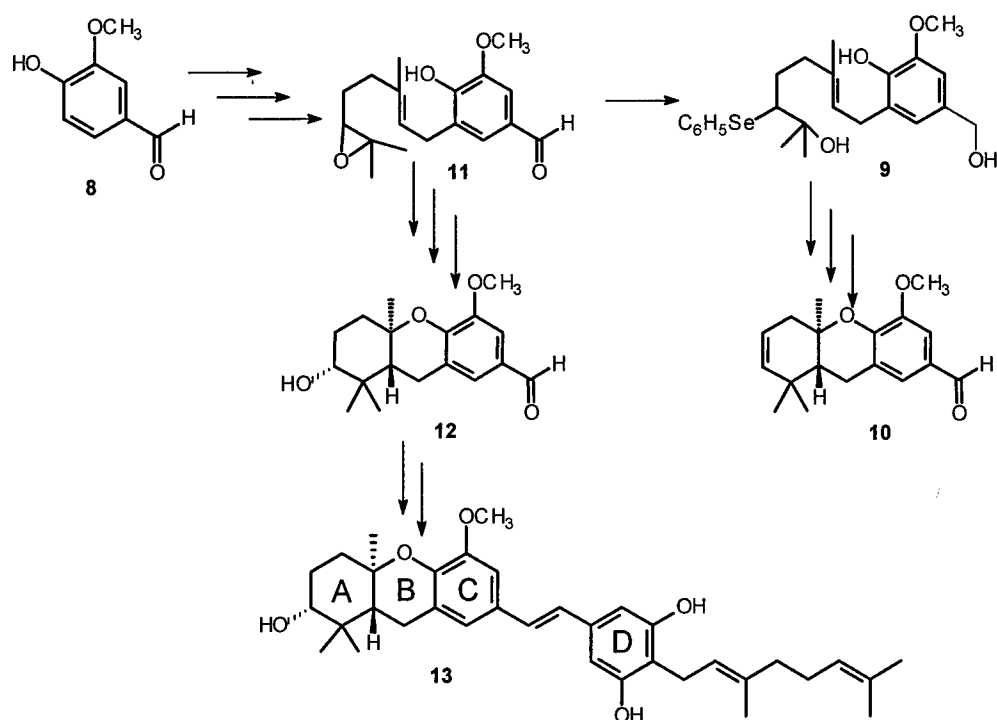


Figure 3. Background synthetic work.

To complete synthesis of a tetracyclic schweinfurthin, aldehyde **12** was condensed with the natural right half synthon, phosphonate **6**. Final deprotection of the resulting stilbene afforded 3-deoxyschweinfurthin B (**13**). This result confirmed the overall synthetic plan and represented the first synthesis of an oxygenated tetracyclic schweinfurthin. Synthetic 3-deoxyschweinfurthin B was tested in the 60 cell-line assay and to our great satisfaction was found to have activity (0.20 μM) very comparable to that of the natural products. Even more importantly the differential activity across the cell-lines was correlated with the natural schweinfurthins A/B? (correlation coefficient = 0.75, Figure 4), suggesting that the synthetic compound was operating at the same, and as yet unknown, molecular or cellular target. Thus the opportunity to explore the effect of right half modifications on the bioactivity and physical properties of the schweinfurthins was

presented. In addition to this structure activity information, such studies might help to identify and overcome a tendency toward decomposition noted during the isolation of the tetracyclic natural products and observed with the synthetic 3-deoxyschweinfurthin B as well. The origin

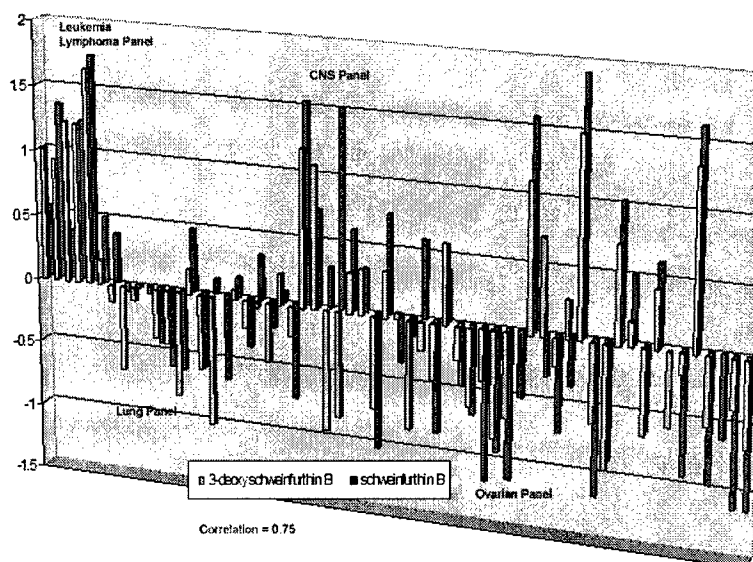


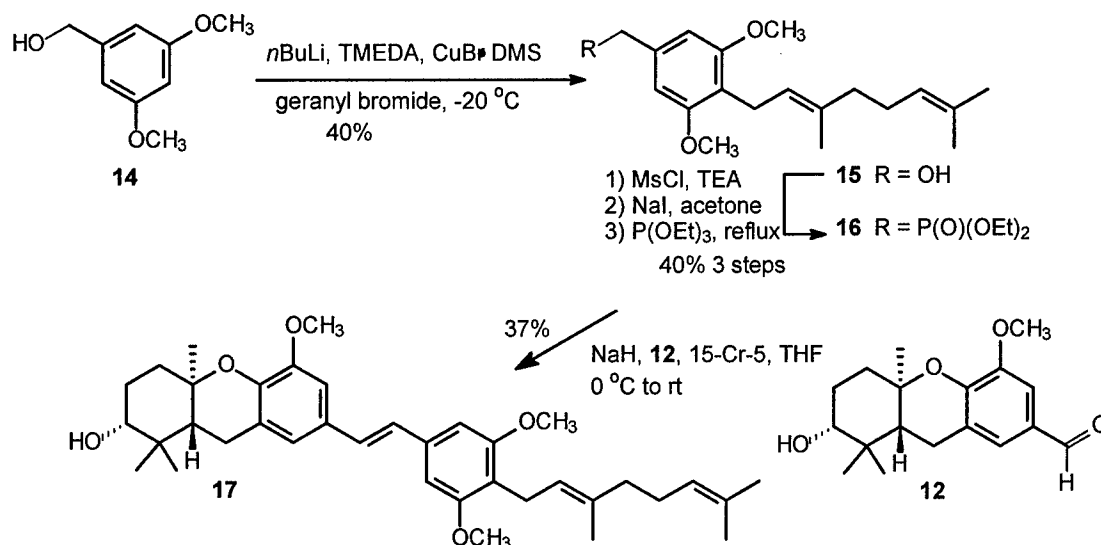
Figure 4. Mean graph comparison of 3-deoxyschweinfurthin B (13) and schweinfurthin B (2). Deviations from the mean in log units against each cell line measured in the NCI 60 cell-line assay at the GI_{50} level, data is presented so that positive deviations indicate more potent cytotoxicity. Approximate regions of several sub-panels are indicated. Complete 60 cell-line data is presented in the supplemental material.

of this lability was presumed to be the resorcinol moiety and that assumption might be verified through the synthesis of analogues. Finally, preparation of a series of analogues might allow identification of a point to introduce functionality that ultimately would allow mechanism of action studies.¹²

Chemical Synthesis

Dimethoxy-3-deoxyschweinfurthin B (17) was selected as the first target of these studies. A path to the requisite phosphonate 16 commenced with the commercial benzyl

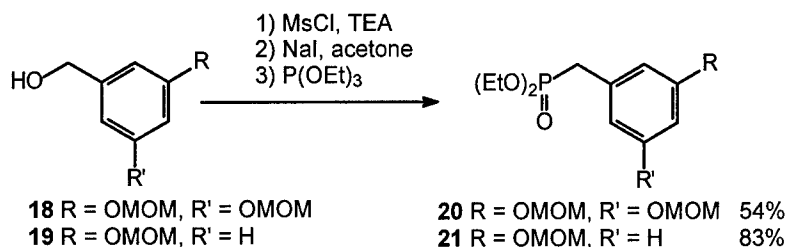
alcohol **14** (Scheme 1). Alkylation of this alcohol by treatment with 2-3 equivalents of strong base and subsequent reaction of the presumed dianion intermediate with geranyl bromide gave the geranylated arene **15** in modest yield. While modest in this case, the yield from this approach is comparable to those where the benzylic alcohol was protected,¹³ and this strategy leads to considerable savings in time and materials. Subsequent introduction of the phosphonate via Arbuzov reaction of the iodide, itself the result of displacement of the mesylate, smoothly gave the desired benzylic phosphonate **16** in 4 steps and 16% overall yield. Modified HWE coupling¹⁴ of phosphonate **16** with aldehyde **12** afforded the desired dimethoxy-3-deoxyschweinfurthin B (**17**) in modest yield.



Scheme 1.

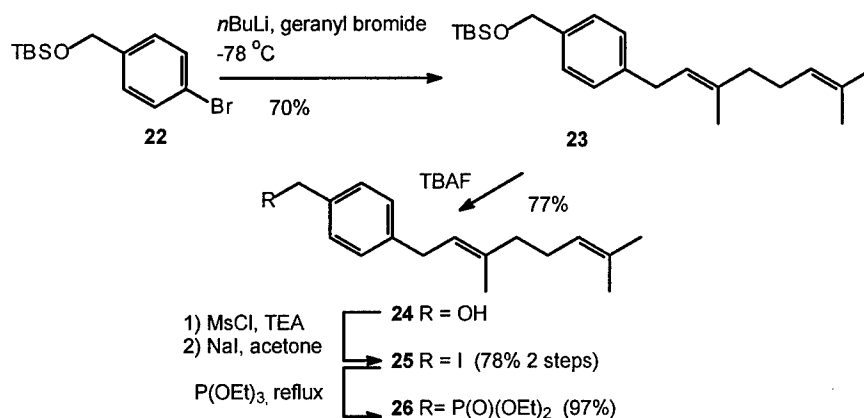
Using very similar chemistry phosphonates **20** and **21** were synthesized (Scheme 2). Thus known methoxymethyl protected benzylic alcohols **18**¹⁵ and **19**¹⁶ were subjected to a three step protocol including preparation of the mesylates, conversion to

the corresponding iodides, and Arbuzov reactions. The desired phosphonates **20** and **21** were isolated in satisfactory yields.



Scheme 2.

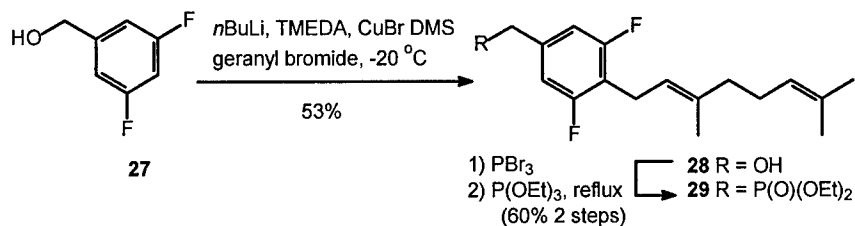
The phosphonate **26** (Scheme 3), which lacks both of the resorcinol hydroxyl groups was obtained by alkylation of the organolithium reagent derived by halogen metal exchange of known aryl bromide **22**.¹⁷ The resulting geranylated arene **23** was then allowed to react with fluoride ion to remove the silyl ether protecting group and afford benzylic alcohol **24**. A parallel series of three steps was used to convert alcohol **24** to the phosphonate **26** in excellent yield.



Scheme 3.

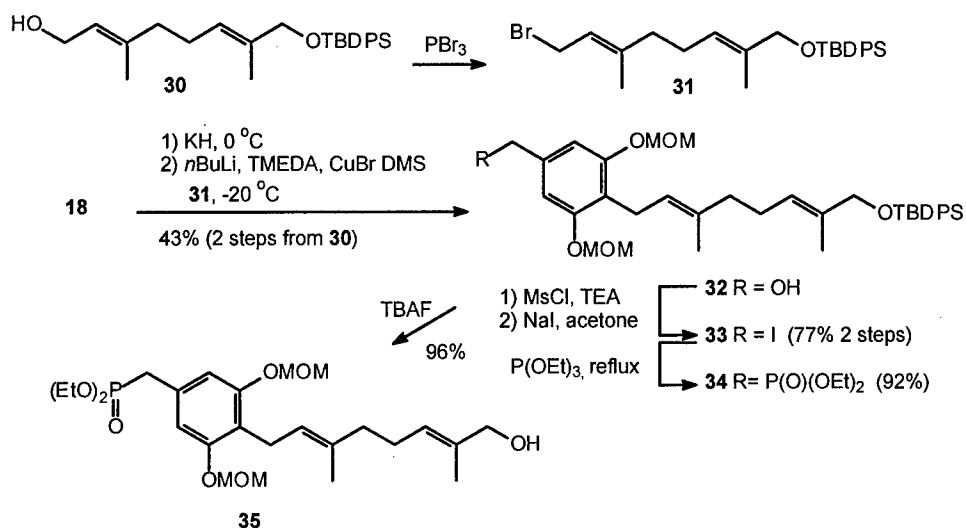
Difluorophosphonate **29** was synthesized from the commercial difluoro benzylic alcohol **27** (Scheme 4). Treatment of this alcohol under the optimized DoM conditions, and alkylation of the resulting dianion, afforded the arene **28** in moderate yield. A two

step reaction sequence involving transformation into the benzylic bromide and Arbuzov reaction with triethylphosphite gave the desired phosphonate **29**.



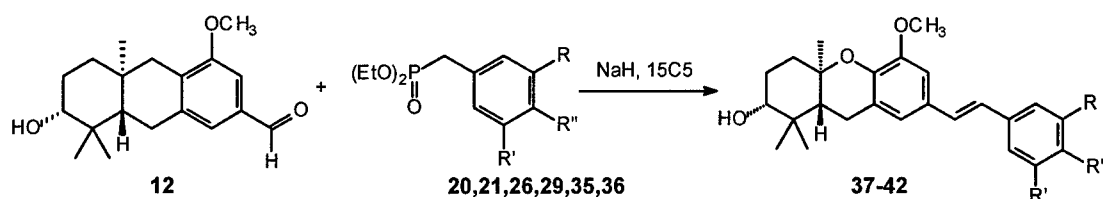
Scheme 4

To obtain the terminally functionalized phosphonate **35**, the requisite allyl bromide **31** was synthesized from the known silyl ether **30**¹⁸ by treatment with PBr_3 . The benzylic alcohol **18** (Scheme 5) then was treated with KH followed by DoM and alkylation with the allylic bromide **31** to afford arene **32**. The standard sequence of transformations, from the benzylic alcohol to the iodide followed by displacement with triethylphosphite, gave the protected phosphonate **34**. This was subjected to reaction with TBAF under standard conditions to effect removal of the silyl ether and afford the desired phosphonate **35** in excellent yield.



Scheme 5.

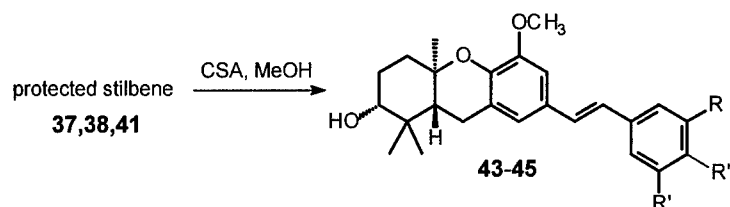
With a representative group of phosphonates in hand, exploration of the required HWE couplings was initiated. Phosphonates **20**, **21**, **26**, **29**, **35** and the commercial phosphonate **36** were allowed to react with aldehyde **12** (Scheme 6, Table 1) under conditions parallel to those employed to synthesize dimethoxy-3-deoxyschweinfurthin B (**17**, *vide supra*). These reactions afforded the expected stilbenes **37-42** in moderate to excellent yields. These HWE couplings have been found reliable in the presence of the unprotected A-ring hydroxyl group, thus avoiding potentially problematic protection/deprotection sequences. Finally, the stilbenes **37**, **38**, and **41** were treated with camphorsulfonic acid (CSA) in methanol¹⁹ to free the resorcinol hydroxyl groups (Scheme 7, Table 2) and afford the desired compounds **43-45**.



Scheme 6.

Phosphonate	Substituents	Stilbene	yield
20	R = R' = OMOM, R'' = H	37	91%
21	R = OMOM, R' = R'' = H	38	62%
26	R = R' = H, R'' = C ₁₀ H ₁₇	39	55%
29	R = R' = F, R'' = C ₁₀ H ₁₇	40	85%
35	R = R' = OMOM, R'' = C ₁₀ H ₁₆ OH	41	60%
36	R = R' = R'' = H	42	90%

Table 1.



Scheme 7.

Protected Stilbene	Product	Yield
37	43 R = R' = OMOM, R'' = H	93%
38	44 R = OMOM, R' = R'' = H	63%
41	45 R = R' = OMOM, R'' = C ₁₀ H ₁₆ OH	42%

Table 2.

Results and Discussion

The seven target schweinfurthin analogs **17**, **39**, **40**, **42-45** were tested at the NCI in the 60 cell line cytotoxicity screen. Every compound tested showed some cytotoxic effects (Table 3), with mean GI₅₀'s ranging from 42 μ M for the difluoro analog **40**, to 1.0 μ M for the analog with the modified geranyl chain **45**. Of special significance however was the pattern of activity for the compounds tested.

Our initial hypothesis was that the pharmacophore for differential activity in this family resided within the left half of the molecule. [?This seems reasonable based on the activity differences within the natural members of the family with schweinfurthin C (**3**) bearing an identical right half resorcinol substructure displaying essentially no differential correlated cytotoxicity whereas the hexahydroxanthenes schweinfurthin A (**1**) and B (**2**) show highly differential activity against the various cell lines.?] The dimethoxy derivative **17** was targeted with the hope that it would be more stable and still retain the cytotoxic profile of the family. Unfortunately, this proved not to be the case.

Compound	13	43	45	40	42	39	17	44	1	2	Log (mean GI ₅₀)
13	1.00										-6.13
43	0.50	1.00									-5.11
45	0.80	0.42	1.00								-5.99
40	-0.05	0.04	0.02	1.00							-4.38
42	0.31	0.24	0.50	0.00	1.00						-4.81
39	0.01	0.10	0.15	0.59	0.30	1.00					-4.73
17	0.39	0.42	0.34	0.08	0.15	0.34	1.00				-5.18
44	0.65	0.45	0.62	-0.08	0.25	-0.08	0.18	1.00			-5.42
1	0.75	0.38	0.74	-0.07	0.31	0.12	0.46	0.64	1.00		-6.40
2	0.75	0.46	0.78	-0.17	0.29	0.05	0.42	0.72	0.91	1.00	-6.10

Table 3. Cytotoxic activity of the schweinfurthin analogs at the GI₅₀ level and the correlation matrix for the 60 cell-line assay for the entire schweinfurthin family data.

Instead, dimethoxy-3-deoxyschweinfurthin B (**17**) was 10 fold less cytotoxic than the parent 3-deoxyschweinfurthin B. More intriguing was the differential cytotoxicity displayed by this analog (Figure 5). While displaying some differential activity across the tested cell lines, the pattern was not as well correlated with the natural product (correlation coefficient = 0.42 vs. **2**) as was that of 3-deoxyschweinfurthin B (correlation coefficient = 0.75 vs. **2**, Table 4). Clearly this result shows that methylation of the phenols is not well-tolerated but these findings also raise a question of how they function within the pharmacophore.

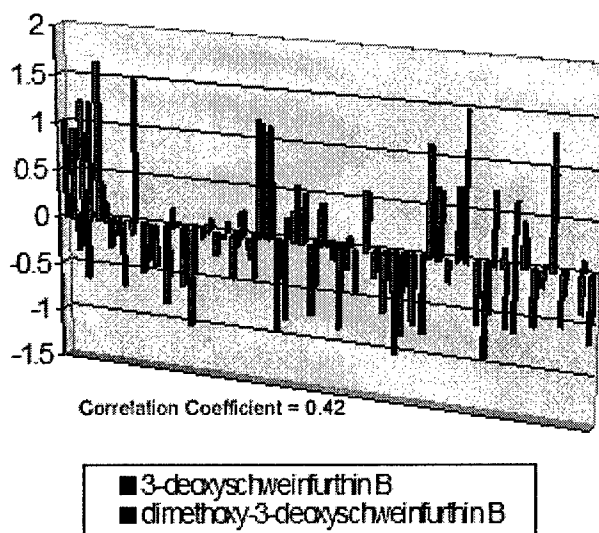


Figure 5. Mean graph comparison of 3-deoxyschweinfurthin B (**13**) and dimethoxy- 3-deoxyschweinfurthin B (**17**). Deviations from the mean in log units against each cell line measured in the NCI 60 cell-line assay at the GI₅₀ level, data is presented so that positive deviations indicate more potent cytotoxicity. Complete 60 cell line data is available in the supplemental material.

To probe the activity of other H-bond acceptors in the D-ring, the difluorinated compound **40** was tested. This compound was found to have the weakest antitumor activity of all the analogs tested so far, as well as a total lack of correlation to the activity

of the natural products (correlation coefficient = -0.17 vs. **2**). The results of these two assays highlight the importance of this right half substructure to differential activity. A further test of this theory involved compounds **39** and **42**, both of which lack the resorcinol oxygens. Both compounds show very weak cytotoxicity (mean GI₅₀'s of 19 and 15 μ M respectively), and virtually no correlation to the natural product (correlation coefficients 0.05 and 0.29 respectively vs. **2**).

Once the importance of the hydroxyl hydrogen was identified, implicating this substructure as a hydrogen bond donor in the pharmacophore, it was intriguing to ascertain the requirements for the geranyl chain. Schweinfurthin D (**4**) which shows similar cytotoxicity to schweinfurthin B (**2**) possesses a hydrated terminal olefin that would seem to indicate a region with some tolerance to modification. This would be of crucial importance in efforts to attach an active schweinfurthin to an affinity reagent or other probe for studies aimed at elucidation of their cellular target(s). As a first step towards deciphering the role of the geranyl chain it seemed appropriate to test if simple deletion of this substructure would affect the activity.

Compound **43**, lacking the geranyl chain, was shown to be ~30 times less active (mean GI₅₀ = 7.8 μ M) than 3-deoxyschweinfurthin B (**13**). It does however show some degree of correlation in pattern of differential activity (correlation coefficient = 0.46 vs. **2**) with the natural product. This result reveals the opportunity to install other motifs at this position with a goal of finding a potential affinity probe. Compound **43** still does show the same propensity towards degradation as the other stilbenes bearing the resorcinol hydroxyl groups. Because a formal deletion of one of the D-ring hydroxyl groups might be expected to improve the phenol **44** was tested and found to be two-fold

more cytotoxic than resorcinol **43** (mean GI_{50} = 3.8 μ M). Even more importantly, phenol **44** was found to have differential activity highly correlated with that of the natural product (correlation coefficient = 0.72).

Based on these results a partial pharmacophore could be recognized. At least one of the D-ring hydroxyl groups was crucial to activity, whereas the geranyl chain was a clearly amenable to some modification. In order to test our hypothesis of using the terminus of the geranyl system as a point of attachment to some form of affinity reagent, it would be necessary to append some form of reactive functional group to this position. This was realized in the analog **45** which contains an allylic alcohol at the trans position of the geranyl chain terminus. Gratifyingly this compound showed very good activity. It was essentially equipotent with schweinfurthin B (mean GI_{50} = 1.0 μ M) and this activity was highly correlated to the natural product (correlation coefficient = 0.78 vs. 2).

Conclusions

The schweinfurthin family of natural products offers a rare opportunity in the field of cytotoxic natural products. Their profile of activity across the NCI 60 cell line assay indicates these agents may act at a novel and as yet untapped mechanism of action against the susceptible tumor cell lines. The current studies encourage further testing of these compounds by making available synthetic analogs with high activity and more favorable chemical properties than the natural products. Finding highly correlated activity in the phenol analog **44** should lead to much less labile schweinfurthins and to more predictable supplies of these agents for the next stages of testing. Synthetic analog **45** which displays highly correlated and potent activity is suitable for studies leading to

the attachment of affinity reagents to probe the mechanism of action of this family of cytotoxins. Further work in these areas will be disclosed in due course.

Experimental

[4-(3,7-Dimethyl-octa-2,6-dienyl)-3,5-dimethoxy-phenyl]-methanol (15) *n*BuLi (0.87 mL, 2.15 M in hexanes) was added dropwise to a solution of benzylic alcohol **14** (105 mg, 0.62 mmol) and TMEDA (0.28 mL, 1.9 mmol) in THF (10 mL) at $-20\text{ }^{\circ}\text{C}$. After the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for 1 h, CuBr as its DMS complex (255 mg, 1.24 mmol) was added in one portion and the solution was stirred for 1 h at $-20\text{ }^{\circ}\text{C}$. Geranyl bromide (0.15 mL, 0.76 mmol) in THF (5 mL) was added *via* syringe and the reaction mixture was stirred for 2 h at $-20\text{ }^{\circ}\text{C}$. The reaction was quenched by addition of 1N NH_4Cl , the aqueous layer was neutralized to pH 7 with 1N HCl, and this layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO_4), and concentrated *in vacuo*. Final purification of the residue by flash column chromatography (20% EtOAc in hexanes) afforded alcohol **15** (76 mg, 40%) as a clear oil. ^1H NMR δ 6.54 (s, 2H), 5.17–5.12 (tm, $J = 7.1\text{ Hz}$, 1H), 5.07–5.02 (tm, $J = 6.9\text{ Hz}$, 1H), 4.63 (s, 2H), 3.80 (s, 6H), 3.31 (d, $J = 7\text{ Hz}$, 2H), 2.04–1.89 (m, 4H), 1.74 (s, 3H), 1.63 (s, 3H), 1.55 (s, 3H); ^{13}C NMR δ 160.3 (2C), 141.8, 136.8, 133.2, 126.6, 124.8, 119.9, 104.7 (2C), 68.0, 57.9 (2C), 41.9, 28.9, 27.8, 24.2, 19.8, 18.1. Anal. Calcd for $\text{C}_{19}\text{H}_{28}\text{O}_3$: C, 74.96; H, 9.27. Found: C, 74.82; H, 9.34.

[4-(3,7-dimethyl-octa-2,6-dienyl)-3,5-dimethoxy-benzyl]-phosphonic acid diethyl ester (16) Methanesulfonyl chloride (0.15 mL, 1.94 mmol) was added dropwise to a solution of alcohol **15** (181 mg, 0.59 mmol) and Et_3N (0.3 mL 1.9 mmol) in CH_2Cl_2 (5

mL) and the solution was stirred for 2 h at 0 °C. The reaction mixture was allowed to warm to rt over 5 h, quenched by addition of H₂O, and extracted with EtOAc. The combined organic layers were washed with NH₄Cl (sat), brine, dried (MgSO₄), and concentrated *in vacuo*. The resulting residue and NaI (310 mg, 2.06 mmol) were stirred in acetone (8 mL) for 24 h. The reaction mixture was concentrated *in vacuo* to afford a red solid, which was dissolved in EtOAc. After the resulting yellow solution was washed once with NaHCO₃ and then with Na₂S₂O₃ until the color faded, it was extracted with ether and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The resulting yellow oil was added to triethyl phosphite (1.5 mL) and the mixture was heated at 100 °C for 20 h. After the solution was allowed to cool to rt, it was poured into ether (5 mL). The mixture was extracted with ether, dried (MgSO₄), and concentrated *in vacuo*. The initial yellow oil was purified by flash chromatography (50% EtOAc in hexanes) to afford phosphonate **16** (73 mg, 40%) as a light yellow oil: ¹H NMR δ 6.49 (d, *J* = 2.4 Hz, 2H), 5.18–5.13 (tm, *J* = 7.3 Hz, 1H), 5.07–5.02 (tm, *J* = 6.8 Hz, 1H), 4.09–3.98 (m, 4H), 3.80 (s, 6H), 3.31 (d, *J* = 7.0 Hz, 2H), 3.11 (d, *J*_{PH} = 21.5 Hz, 2H), 2.06–1.94 (m, 4H), 1.82 (s, 3H), 1.68 (s, 3H), 1.56 (s, 3H), 1.27 (tm, *J* = 7.0 Hz, 6H); ¹³C NMR δ 160.9 (d, *J*_{CP} = 3.1 Hz, 2C), 137.5, 134.1, 132.9 (d, *J*_{CP} = 9.0 Hz), 127.5, 125.7 (d, *J*_{CP} = 2.9 Hz), 120.1 (d, *J*_{CP} = 3.4 Hz), 108.6 (d, *J*_{CP} = 6.7 Hz, 2C), 65.1 (d, *J*_{CP} = 6.7 Hz, 2C), 58.7 (2C), 42.8, 37.1 (d, *J*_{CP} = 137.3 Hz), 29.7, 28.6, 24.9, 20.6, 19.4 (d, *J*_{CP} = 6.0 Hz, 2C), 18.9; ³¹P NMR δ +26.4; HRMS (EI) calcd for C₂₃H₃₇O₅PNa [M⁺ + Na], 447.2276; found 447.2265.

Dimethoxy-3-deoxyschweinfurthin B (17). A solution of phosphonate **16** (20 mg, 0.04 mmol) and aldehyde **12** (10 mg, 0.03 mmol) in THF (1.5 mL) was added to a suspension

of NaH (29 mg, 0.71 mmol, 60% suspension in oil) and 15C5 (4 μ L, 22 nmol) in THF (2.5 mL) at 0 °C. The resulting mixture was allowed to come to rt and stir for 20 hours. The solution was quenched with water, extracted (ether), and the combined organic layers were washed with brine. The residual organic layer was dried (MgSO₄), and concentrated in vacuo to give a yellow oil. Final purification by column chromatography (1:1 hexanes:EtOAc) afforded the target schweinfurthin analog **17** (6.4 mg, 37%) as a clear oil: ¹H NMR δ 6.95 – 6.88 (m, 4H), 6.67 (s, 2H), 5.19 (t, J = 6.8 Hz, 1H), 5.07 (t, J = 5.7 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 6H), 3.46 – 3.44 (m, 2H), 3.36 – 3.33 (m, 1H), 2.75 – 2.72 (m, 2H), 2.21 – 1.75 (m, 9H), 1.77 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H), 1.27 (s, 3H), 1.10 (s, 3H), 0.89 (s, 3H); HREIMS calcd for C₃₇H₅₀O₅ (M⁺) 574.3658, found 574.3651.

(3,5-bis-Methoxymethoxy-benzyl)-phosphonic acid diethyl ester (20).

Methanesulfonyl chloride (1.4 mL, 18.1 mmol) was added dropwise to a stirred solution of alcohol **18** (881 mg, 3.9 mmol) and Et₃N (2.2 mL 15.76 mmol) in CH₂Cl₂ (150mL). The solution was stirred for 2 h at 0 °C. The reaction mixture was allowed to warm to rt over 5 h, quenched by addition of water, and extracted with EtOAc. The combined organic layers were washed with NH₄Cl (sat), brine, dried (MgSO₄), and concentrated *in vacuo*. The yellow residue was treated with NaI (2.33 g, 15.6 mmol) in acetone (20 mL) for 24 h at rt. The reaction mixture was concentrated *in vacuo* to a red solid, which was dissolved in EtOAc. After the resulting yellow solution was washed once with NaHCO₃ and then with Na₂S₂O₃ until the color faded, it was extracted with ether and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Final purification of the residue by flash column chromatography (30% EtOAc in hexanes) afforded compound iodide (1.12 g, 84%) as a yellow oil: ¹H NMR δ 6.73 (d, J = 2.2 Hz,

2H), 6.63 (t, $J = 2.2$ Hz, 1H), 5.2 (s, 4H), 4.4 (s, 2H), 3.5 (s, 6H); ^{13}C NMR δ 158.5 (2C), 141.5, 110.3 (2C), 104.7, 94.7 (2C), 56.3 (2C), 5.5; HRMS (EI) calcd for $\text{C}_{11}\text{H}_{15}\text{O}_4\text{I}$ [M^+], 338.0015; found 338.0016. A stirred solution of this iodide (1.11 g, 3.3 mmol) in triethyl phosphite (2.5 mL) was heated at reflux for 9 h, then it was allowed to cool to rt and poured into ether (8 mL). The resulting mixture was extracted with ether, dried (MgSO_4) and concentrated *in vacuo*. Final purification of the residue by flash chromatography (gradient, 30–80% EtOAc in hexanes) afforded phosphonate **20** (734 mg, 64%) as a light yellow oil: ^1H NMR δ 6.58–6.55 (m, 3H), 5.06 (s, 4H), 3.97 (m, 4H), 3.39 (s, 6H), 3.01 (d, $J_{\text{PH}} = 21.6$ Hz, 2H), 1.20 (tm, $J = 7.1$ Hz, 6H); ^{13}C NMR δ 158.2 (d, $J_{\text{CP}} = 3.2$ Hz, 2C), 133.8 (d, $J_{\text{CP}} = 8.8$ Hz), 111.2 (d, $J_{\text{CP}} = 6.5$ Hz, 2C), 103.5 (d, $J_{\text{CP}} = 3.4$ Hz), 94.4 (2C), 62.1 (d, $J_{\text{CP}} = 6.6$ Hz, 2C), 55.9 (2C), 33.9 (d, $J_{\text{CP}} = 138.1$ Hz), 16.3 (d, $J_{\text{CP}} = 6.1$ Hz, 2C); ^{31}P NMR δ +25.7. Anal. Calcd for $\text{C}_{15}\text{H}_{25}\text{O}_7\text{P}$: C, 51.72; H, 7.23. Found: C, 51.55; H, 7.27.

(3-Methoxymethoxy-benzyl)-phosphonic acid diethyl ester (21) Methanesulfonyl chloride (1.0 mL, 12.9 mmol) was added dropwise to a solution of alcohol **19** (500 mg, 2.97 mmol) and Et_3N (0.5 mL 3.6 mmol) in CH_2Cl_2 (10 mL) and the solution was stirred for 2 h at 0 °C. The reaction mixture was allowed to warm to rt over 5 h, quenched by addition of H_2O , and extracted with EtOAc. The combined organic layers were washed with NH_4Cl (sat), brine, dried (MgSO_4), and concentrated *in vacuo*. The resulting yellow residue was treated with NaI (1 g, 3.6 mmol) in acetone (15 mL) for 24 h at rt. This reaction mixture was concentrated *in vacuo* to afford a red solid, which was dissolved in EtOAc. After the resulting yellow solution was washed once with NaHCO_3 and then with $\text{Na}_2\text{S}_2\text{O}_3$ until the color faded, it was extracted with ether and the combined organic

layers were dried (MgSO₄) and concentrated *in vacuo*. The resulting yellow oil was added to triethyl phosphite (4 mL) and the solution was heated at 100 °C for 20 h. After the solution was allowed to cool to rt, it was poured into ether (10 mL). The mixture was extracted with ether, dried (MgSO₄), and concentrated *in vacuo*. The initial yellow oil was purified by flash chromatography (50% EtOAc in hexanes) to afford phosphonate **21** (709 mg, 83%) as a light yellow oil: ¹H NMR δ 7.20 (tr, *J* = 7.9 Hz, 1H), 7.08-6.89 (m, 3H), 5.17 (s, 2H), 4.15-3.97 (m, 4H), 3.44 (s, 3H), 3.11 (d, *J*_{PH} = 21.6 Hz, 2H), 1.27–1.22 (m, 6H); ¹³C NMR δ 157.1 (d, *J*_{CP} = 3.2 Hz), 132.9 (d, *J*_{CP} = 8.9 Hz), 129.2 (d, *J*_{CP} = 3.1 Hz), 123.1 (d, *J*_{CP} = 6.5 Hz), 117.5 (d, *J*_{CP} = 6.5 Hz), 114.5 (d, *J*_{CP} = 3.5 Hz), 94.1, 61.8 (d, *J*_{CP} = 6.7 Hz, 2C), 55.6, 33.4 (d, *J*_{CP} = 137.2 Hz), 16.1 (d, *J*_{CP} = 6.0 Hz, 2C); ³¹P NMR δ +25.8. Anal. Calcd for C₁₃H₂₁O₅P: C, 54.16; H, 7.34. Found: C, 53.98; H, 7.35.

***tert*-Butyl-[4-(3,7-dimethyl-octa-2,6-dienyl)-benzyloxy]-dimethyl-silane (23)** *n*BuLi (7.90 mL, 2.5 M in hexane, 19.8 mmol) was added dropwise to a stirred solution of aryl bromide **22** (3.13 g, 10.4 mmol) in THF (15 mL) over 15 min at –78 °C. The reaction mixture was allowed to stir for 2 h at –78 °C. Geranyl bromide (2.5 mL, 12.6 mmol) was added dropwise and the reaction mixture was stirred for 2 h at –78 °C. The reaction mixture was allowed to warm to rt, was quenched by addition of H₂O, and then was extracted with ether. The combined organic layers were washed with NH₄Cl (sat), brine, dried (MgSO₄), and concentrated *in vacuo*. Final purification of the residue by flash column chromatography (hexanes) afforded compound **23** (2.61 g, 70%) as a light yellow oil: ¹H NMR δ 7.24-7.19 (m, 2H), 7.14-7.12 (m, 2H), 5.43–5.38 (tm, *J* = 7.4 Hz, 1H), 5.20–5.15 (tm, *J* = 7.5 Hz, 1H), 4.77 (s, 2H), 3.41 (d, *J* = 7.4 Hz, 2H), 2.19–2.09 (m, 4H), 1.77 (s, 3H), 1.75 (s, 3H), 1.67 (s, 3H), 1.01 (s, 9H), 0.16 (s, 6H); ¹³C NMR δ. 140.6,

140.0, 136.3, 131.6, 128.4 (2C), 126.4 (2C), 124.5, 123.4, 65.1, 39.9, 34.1, 26.8, 26.2 (3C), 25.9, 18.6, 17.9, 16.3, -5.0 (2C). Anal. Calcd for $C_{23}H_{38}OSi$: C, 77.01; H, 10.68. Found: C, 77.08; H, 10.69.

[4-(3,7-Dimethyl-octa-2,6-dienyl)-phenyl]-methanol (24) TBAF (26.0 mL, 1.0 M in THF, 26.0 mmol) was added dropwise to a stirred solution of protected alcohol **23** (2.56 g, 7.14 mmol) in THF (20 mL). The solution was stirred for 2 h at 0 °C and then was allowed to warm to rt over 5 h. The reaction was quenched by addition of NH_4Cl (sat), and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification of the residue by flash column chromatography (20% EtOAc in hexanes) afforded compound **24** (1.35 g, 77%) as a light yellow oil: 1H NMR δ 7.28-7.24 (m, 2H), 7.18-7.15 (m, 2H), 5.35-5.30 (tm, $J = 7.2$ Hz, 1H), 5.12-5.08 (tm, $J = 6.7$ Hz, 1H), 4.63 (s, 2H), 3.35 (d, $J = 7.3$ Hz, 2H), 2.12-2.02 (m, 4H), 1.70 (s, 1H exchanges with D_2O), 1.70 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR δ 141.6, 138.5, 136.5, 131.7, 128.7 (2C), 127.4 (2C), 124.4, 123.1, 65.4, 39.9, 34.1, 26.8, 26.0, 17.9, 16.3; HRMS (EI) calcd for $C_{17}H_{24}O$ [M^+], 244.1827; found 244.1832.

1-(3,7-Dimethyl-octa-2,6-dienyl)-4-iodomethyl-benzene (25) Methanesulfonyl chloride (1.8 mL, 23.3 mmol) was added dropwise to a stirred solution of alcohol **24** (1.27 g, 5.22 mmol) and Et_3N (3 mL 21.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C over 2 h. The reaction mixture was allowed to warm to rt over 5 h. After the reaction was quenched by addition of water, it was extracted with EtOAc. The combined organic layers were washed with NH_4Cl (sat), brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting yellow residue was treated with NaI (3.51 g, 23.4 mmol) in acetone (20 mL) at rt for 24 h. The reaction mixture was concentrated *in vacuo* to afford a red solid, which

was dissolved in EtOAc. After the resulting solution was washed once with NaHCO_3 and then with $\text{Na}_2\text{S}_2\text{O}_3$ until the color faded, the aqueous layer was extracted with ether and the combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. Final purification of the residue by flash column chromatography (20% EtOAc in hexanes) afforded compound **25** (1.44 g, 78%) as a yellow oil: ^1H NMR δ 7.30–7.24 (m, 2H), 7.11–7.08 (m, 2H), 5.35–5.30 (tm, $J = 7.2$ Hz, 1H), 5.14–5.09 (tm, $J = 6.6$ Hz, 1H), 4.47 (s, 2H), 3.33 (d, $J = 7.2$ Hz, 2H), 2.14–2.03 (m, 4H), 1.71 (s, 6H), 1.61 (s, 3H); ^{13}C NMR δ 141.9 (2C), 136.8, 131.7, 129.0 (2C), 128.9 (2C), 124.4, 122.8, 39.9, 34.1, 26.8, 26.0, 17.9, 16.3, 6.4; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{23} [\text{M}^+ - \text{I}]$, 227.1800; found 227.1801.

Diethyl[4-(3,7-dimethyl-octa-2,6-dienyl)-benzyl]phosphonate (26) A stirred solution of iodide **25** (1.35g, 3.82 mmol) in triethyl phosphite (25 mL) was heated at reflux for 4 h, and then allowed to cool to rt. Excess triethyl phosphite was removed by vacuum distillation and the resulting yellow oil was purified by flash chromatography (30% EtOAc in hexanes) to afford phosphonate **26** (1.34 g, 97%) as a light yellow oil: ^1H NMR δ 7.22–7.18 (m, 2H), 7.12–7.09 (m, 2H), 5.33–5.29 (tm, $J = 7.2$ Hz, 1H), 5.11–5.08 (tm, $J = 6.6$ Hz, 1H), 4.06–4.00 (m, 4H), 3.32 (d, $J = 7.2$ Hz, 2H), 3.11 (d, $J_{\text{PH}} = 21.3$ Hz, 2H), 2.12–2.05 (m, 4H), 1.69 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.24 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR δ 140.6 (d, $J_{\text{CP}} = 3.8$ Hz), 136.5, 131.7, 129.8 (d, $J_{\text{CP}} = 6.5$ Hz, 2C), 128.9 (d, $J_{\text{CP}} = 9.3$ Hz), 128.7 (d, $J_{\text{CP}} = 3.1$ Hz, 2C), 124.5, 123.1, 62.2 (d, $J_{\text{CP}} = 6.8$ Hz, 2C), 39.9, 34.4, 32.6 (d, $J_{\text{CP}} = 138.2$ Hz), 26.8, 26.0, 17.9, 16.6 (d, $J_{\text{CP}} = 6.1$ Hz, 2C), 16.3; ^{31}P NMR δ +26.6. Anal. Calcd for $\text{C}_{21}\text{H}_{33}\text{O}_3\text{P}$: C, 69.21; H, 9.13. Found: C, 69.09; H, 9.16.

[4-(3,7-Dimethyl-octa-2,6-dienyl)-3,5-difluoro-phenyl]-methanol (28) A solution of benzylic alcohol **27** (67 mg, 0.46 mmol) and TMEDA (0.21 mL, 1.4 mmol) in THF (10

mL) was cooled to $-20\text{ }^{\circ}\text{C}$. After *n*BuLi (0.64 mL, 2.15 M in hexanes) was added dropwise and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for 1 h, CuBr as its DMS complex (192 mg, 0.93 mmol) was added in one portion and the solution was stirred for 1 h at $-20\text{ }^{\circ}\text{C}$. A solution of geranyl bromide (0.11 mL, 0.55 mmol) in THF (5 mL) was added to the reaction mixture *via* syringe at $-20\text{ }^{\circ}\text{C}$ and the solution was stirred for 2 h. The reaction was quenched by addition of 1N NH_4Cl , the aqueous layer was neutralized to pH 7 with 1N HCl, and then was extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO_4), and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc in hexanes) afforded alcohol **28** (68 mg, 53%) as a clear oil: ^1H NMR δ 6.91–6.83 (dm, $J_{\text{HF}} = 7.5\text{ Hz}$, 2H), 5.23–5.19 (tm, $J = 7.3\text{ Hz}$, 1H), 5.08–5.03 (tm, $J = 6.8\text{ Hz}$, 1H), 4.65 (d, $J = 5.6\text{ Hz}$, 2H, becomes a singlet at D_2O wash), 3.36 (d, $J = 7.2\text{ Hz}$, 2H), 2.07–1.96 (m, 4H), 1.75 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H); ^{13}C NMR δ 161.6 (dd, $J_{\text{CF}} = 246.9, 9.6\text{ Hz}$, 2C), 141.2 (t, $J_{\text{CF}} = 9.0\text{ Hz}$), 136.8, 131.7, 124.3, 120.7, 116.4 (t, $J_{\text{CF}} = 20.9\text{ Hz}$), 109.4 (dd, $J_{\text{CF}} = 26.6, 8.9\text{ Hz}$, 2C), 54.4 (t, $J_{\text{CF}} = 2.1\text{ Hz}$), 39.8, 26.7, 25.9, 21.5 (t, $J_{\text{CF}} = 2.5\text{ Hz}$), 17.9, 16.2; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{22}\text{F}_2\text{O}$ [M^+], 280.1639; found 280.1639.

[4-(3,7-Dimethyl-octa-2,6-dienyl)-3,5-difluoro-benzyl]-phosphonic acid diethyl ester (29) PBr_3 (0.03 mL, 0.32 mmol) was added dropwise to a solution of alcohol **28** (180 mg, 0.64 mmol) in ether (10 mL) and the solution was stirred for 7 h at $0\text{ }^{\circ}\text{C}$. The reaction mixture was poured into ice water, extracted with ether, and washed with brine. The combined organic layer was dried (MgSO_4), and concentrated *in vacuo*. The resulting yellow oil was added to triethyl phosphite (3 mL) and sodium iodide (62 mg, 0.41 mmol), and the mixture was heated at $100\text{ }^{\circ}\text{C}$ for 30 h. After this solution was

allowed to cool to rt, it was poured into ether (10 mL) and washed with sodium thiosulfate. The mixture was extracted with ether, dried (MgSO₄), and concentrated *in vacuo*. The initial yellow oil was purified by flash chromatography (gradient, 30–80% EtOAc in hexanes) to afford phosphonate **29** (153 mg, 60%) as a light yellow oil: ¹H NMR δ 6.84–6.77 (m, 2H), 5.22–5.17 (tm, *J* = 6.4 Hz, 1H), 5.08–5.03 (tm, *J* = 6.9 Hz, 1H), 4.11–4.00 (m, 4H), 3.35–3.32 (dm, *J* = 7.2 Hz, 2H), 3.11–3.04 (dm, *J*_{PH} = 21.7 Hz, 2H), 2.07–1.92 (m, 4H), 1.74 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H), 1.31–1.24 (tm, *J* = 7.1 Hz, 6H); ¹³C NMR δ 161.4 (ddd, *J*_{CF} = 245.7, 10.0 Hz, *J*_{CP} = 3.5 Hz, 2C), 136.8, 132.0–131.6 (m), 131.7, 124.3, 120.7, 116.0 (td, *J*_{CF} = 20.3 Hz, *J*_{CP} = 3.5 Hz), 112.9–112.5 (m, 2C), 65.5 (d, *J*_{CP} = 6.75 Hz, 2C), 39.8, 33.5 (dd, *J*_{CP} = 139.2 Hz, *J*_{CF} = 1.9 Hz), 26.7, 25.9, 21.4 (t, *J*_{CF} = 1.7 Hz), 17.9, 16.6 (d, *J*_{CP} = 6.00 Hz, 2C), 16.1; ³¹P NMR δ +24.8 (t, *J*_{PF} = 2.3 Hz). Anal. Calcd for C₂₁H₃₁F₂O₃P: C, 62.99; H, 7.80. Found: C, 63.22; H, 7.98.

{4-[8-(*tert*-butyl-diphenyl-silanyloxy)-3,7-dimethyl-octa-2,6-dienyl]-3,5-bis-methoxymethoxy-phenyl}-methanol (32) PBr₃ (0.7 mL, 7.4 mmol) was added dropwise to a solution of alcohol **30** (521 mg, 1.27 mmol) in ether (10 mL) and the solution was stirred for 7 h at 0 °C. The reaction mixture was poured into ice water, extracted with ether, and washed with brine. The combined organic layer was dried (MgSO₄), and concentrated *in vacuo* to give a yellow residue, bromide **31**. A solution of benzylalcohol **18** (305 mg, 1.34 mmol) in THF (5 mL) was added to a stirred suspension of KH (87 mg, 2.2 mmol) in THF (10 mL) and the reaction mixture was stirred for 1 h at 0 °C. After TMEDA (0.4 mL, 2.7 mmol) was added, the solution was cooled to –20 °C, then *n*BuLi (1.87 mL, 2.15 M in hexanes) was added dropwise and the solution was stirred at –20 °C for 1 h. CuBr as its DMS complex (556 mg, 2.7 mmol) was added in

one portion and the solution was stirred for 1 h at $-20\text{ }^{\circ}\text{C}$. Bromide **31** in THF (5 mL) was added to the reaction mixture *via* syringe at $-20\text{ }^{\circ}\text{C}$. After 2 h, the reaction was quenched by addition of 1N NH_4Cl , and the aqueous layer was neutralized to pH 7 with 1N HCl, and extracted with EtOAc. The combined organic layer was washed with brine, dried (MgSO_4), and concentrated *in vacuo*. Final purification by flash column chromatography (20% EtOAc in hexanes) afforded compound **32** (341 mg, 43% from alcohol **30**) as a clear oil: ^1H NMR δ 7.70–7.67 (m, 4H), 7.43–7.35 (m, 6H), 6.79 (s, 2H), 5.43–5.39 (tm, $J = 7.0\text{ Hz}$, 1H), 5.26–5.19 (m, 5H), 4.62 (s, 2H), 4.03 (s, 2H), 3.47 (s, 6H), 3.40 (d, $J = 9\text{ Hz}$, 2H), 2.19–1.96 (m, 4H), 1.81 (s, 3H), 1.59 (s, 3H), 1.06 (s, 9H); ^{13}C NMR δ 156.0 (2C), 140.2, 135.8 (4C), 134.8, 134.2 (2C), 134.1, 129.7 (2C), 127.8 (4C), 124.6, 122.9, 119.6, 106.7 (2C), 94.6 (2C), 69.3, 65.7, 56.2 (2C), 39.8, 27.1 (3C), 26.4, 22.8, 19.5, 16.3, 13.7. Anal. Calcd for $\text{C}_{37}\text{H}_{50}\text{O}_6\text{Si}$: C, 71.81; H, 8.14. Found: C, 71.72; H, 7.98.

***tert*-Butyl-[8-(4-iodomethyl-2,6-bis-methoxymethoxy-phenyl)-2,6-dimethyl-octa-2,6-dienyloxy]-diphenyl-silane (33)** Methanesulfonyl chloride (0.1 mL, 1.3 mmol) was added dropwise to a stirred solution of alcohol **32** (364 mg, 0.62 mmol) and Et_3N (0.2 mL 1.4 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred for 2 h at $0\text{ }^{\circ}\text{C}$. The reaction mixture was allowed to warm to rt over 5 h, quenched by addition of H_2O , and extracted with EtOAc. The combined organic layers were washed with NH_4Cl (sat) and brine, dried (MgSO_4), and concentrated *in vacuo*. The resulting yellow residue was allowed to react with NaI (132 mg, 0.886 mmol) in acetone (8 mL) for 24 h at rt. The reaction mixture was concentrated *in vacuo* to afford a red solid, which was dissolved in EtOAc. After the resulting yellow solution was washed once with NaHCO_3 and then with

Na₂S₂O₃ until the color faded, it was extracted with ether and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Final purification by flash column chromatography (30% EtOAc in hexanes) afforded the iodide **33** (347 mg, 77%) as a yellow oil: ¹H NMR δ 7.77–7.72 (m, 4H), 7.49–7.38 (m, 6H), 6.84 (s, 2H), 5.48–5.44 (tm, *J* = 6.6 Hz, 1H), 5.29–5.19 (tm, *J* = 6.0 Hz, 1H), 5.20 (s, 4H), 4.43 (s, 2H), 4.08 (s, 2H), 3.50 (s, 6H), 3.41 (d, *J* = 7.1 Hz, 2H), 2.30–2.01 (m, 4H), 1.85 (s, 3H), 1.63 (s, 3H), 1.11 (s, 9H); ¹³C NMR δ 155.8 (2C), 138.1, 135.7 (4C), 134.9, 134.1 (2C), 134.0, 129.7 (2C), 127.8 (4C), 124.5, 122.6, 120.2, 108.6 (2C), 94.6 (2C), 69.2, 56.2 (2C), 39.8, 27.0 (3C), 26.3, 22.9, 19.5, 16.3, 13.7, 6.7; HRMS (EI) calcd for C₃₇H₄₉IO₅Si [M⁺], 728.2394; found 728.2395.

{4-[8-(*tert*-Butyl-diphenyl-silanyloxy)-3,7-dimethyl-octa-2,6-dienyl]-3,5-bis-methoxymethoxy-benzyl}-phosphonic acid diethyl ester (34**)** A solution of iodide **33** (68 mg, 0.093 mmol) and sodium iodide (39 mg, 0.26 mmol) in triethyl phosphite (1.5 mL) was heated at 100 °C for 20 h, allowed to cool to rt, and poured into ether (5 mL). The resulting mixture was extracted with ether, dried (MgSO₄), and concentrated *in vacuo*. The initial yellow oil was purified by flash chromatography (50% EtOAc in hexanes) to afford phosphonate **34** (63.5 mg, 92%) as light yellow oil: ¹H NMR δ 7.70–7.67 (m, 4H), 7.42–7.34 (m, 6H), 6.70 (d, *J*_{HP} = 2.3 Hz, 2H), 5.42–5.39 (tm, *J* = 5.7 Hz, 1H), 5.21–5.17 (trm, *J* = 7.0 Hz, 1H), 5.17 (s, 4H), 4.10–4.00 (m, 6H), 3.45 (s, 6H), 3.37 (d, *J* = 7.0 Hz, 2H), 3.09 (d, *J*_{PH} = 21.5 Hz, 2H), 2.14–1.95 (m, 4H), 1.80 (s, 3H), 1.58 (s, 3H), 1.28 (trm, *J* = 7.08 Hz, 6H), 1.06 (s, 9H); ¹³C NMR δ 155.8 (d, *J*_{CP} = 3.2 Hz, 2C), 135.8 (4C), 134.7, 134.1 (2C), 134.0, 130.5 (d, *J*_{CP} = 9.0 Hz), 129.7 (2C), 127.7 (4C), 124.7, 123.0, 118.9 (d, *J*_{CP} = 3.9 Hz), 109.8 (d, *J*_{CP} = 6.6 Hz, 2C), 94.6 (2C), 69.2, 62.3

(d, J_{CP} = 6.7 Hz, 2C), 56.2 (2C), 39.8, 34.1 (d, J_{CP} = 138.3 Hz), 27.0 (3C), 26.5, 22.7, 19.5, 16.6 (d, J_{CP} = 5.8 Hz, 2C), 16.3, 13.6; ^{31}P NMR δ +26.2. Anal. Calcd for $\text{C}_{41}\text{H}_{59}\text{O}_8\text{PSi}$: C, 66.64; H, 8.05. Found: C, 66.58; H, 8.32.

[4-(8-Hydroxy-3,7-dimethyl-octa-2,6-dienyl)-3,5-bis-methoxymethoxy-benzyl]-phosphonic acid diethyl ester (35) TBAF (0.3 mL, 1M in THF, 0.3 mmol) was added to a solution of phosphonate **34** (55.1 mg, 0.075 mmol) in THF (3 mL) and the solution was stirred for 3 h at rt. The reaction was quenched by addition of water and EtOAc, and then extracted with EtOAc. The combined organic layer was washed with brine, dried (MgSO_4), and concentrated *in vacuo*. Final purification of the residue by flash column chromatography (gradient, 60–100% EtOAc in hexanes) afforded compound **35** (36 mg, 96%) as a clear oil: ^1H NMR δ 6.66 (broad s, 2H), 5.30–5.24 (m, 1H), 5.13–5.06 (m, 5H), 4.04–3.97 (m, 4H), 3.83 (s, 2H), 3.42 (s, 6H), 3.32 (d, J = 7.0 Hz, 2H), 3.04 (d, J_{PH} = 21.5 Hz, 2H), 2.07–1.95 (m, 4H), 1.73 (s, 3H), 1.53 (s, 3H), 1.24 (trm, J = 6.8 Hz, 6H); ^{13}C NMR δ 155.8 (d, J_{CP} = 3.4 Hz, 2C), 135.1, 134.1, 130.4 (d, J_{CP} = 9.1 Hz), 125.9, 123.4, 119.1 (d, J_{CP} = 3.9 Hz), 109.9 (d, J_{CP} = 6.6 Hz, 2C), 94.7 (2C), 68.9, 62.3 (d, J_{CP} = 6.7 Hz, 2C), 56.2 (2C), 39.5, 34.0 (d, J_{CP} = 138.3 Hz), 26.1, 22.7, 16.6 (d, J_{CP} = 6.1 Hz, 2C), 16.2, 13.8; ^{31}P NMR δ +26.2; HRMS (EI) calcd for $\text{C}_{25}\text{H}_{41}\text{O}_8\text{P} [\text{M}^+]$, 500.2539; found 500.2531.

7-[2-(3,5-bis-Methoxymethoxy-phenyl)-vinyl]-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (37) To a stirred suspension of NaH (30 mg, 1.3 mmol) and 15C5 (5 μL , 3 mol %) in THF (5 mL) was added phosphonate **20** (25 mg, 0.12 mmol) and aldehyde **12** (20 mg, 0.066 mmol) at 0 °C. The reaction mixture was allowed to warm to rt over 10 h. The reaction was quenched by addition of water, and

extracted with EtOAc. After the combined organic layers were washed with brine, dried (MgSO_4), and concentrated *in vacuo*, final purification by flash column chromatography (50% EtOAc in hexanes) afforded compound **37** (30 mg, 91%) as a clear oil: ^1H NMR δ 7.00 (d, $J = 17.1$ Hz, 1H), 6.90–6.85 (m, 5H), 6.64 (t, $J = 2.1$ Hz, 1H), 5.20 (s, 4H), 3.90 (s, 3H), 3.51 (s, 6H), 3.46–3.42 (m, 1H), 2.76–2.74 (m, 1H), 2.73–2.71 (m, 1H), 2.17–2.11 (m, 1H), 1.91–1.81 (m, 2H), 1.75–1.54 (m, 2H), 1.27 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 158.7 (2C), 149.2, 143.0, 140.1, 129.6, 128.9, 126.2, 122.8, 120.9, 107.8 (2C), 107.3, 104.1, 94.7 (2C), 78.2, 77.3, 55.3 (2C), 56.2, 46.9, 38.6, 37.9, 28.5, 27.6, 23.4, 20.1, 14.5; HRMS (EI) calcd for $\text{C}_{29}\text{H}_{38}\text{O}_7$ [M^+], 498.2618; found 498.2608.

5-Methoxy-7-[2-(3-methoxymethoxy-phenyl)-vinyl]-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (38). To a stirred suspension of NaH (27 mg, 0.68 mmol) and 15C5 (5 μL , 3 mol %) in THF was added phosphonate **21** (50 mg, 0.173 mmol) and aldehyde **12** (20 mg, 0.066 mmol) at 0 $^\circ\text{C}$ and the reaction mixture was allowed to warm to rt over 10 h. The reaction was quenched by addition of water and extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO_4), and concentrated *in vacuo*. Final purification of the residue by flash column chromatography (50% EtOAc in hexanes) afforded compound **38** (18 mg, 62%) as a clear oil: ^1H NMR δ 7.29–6.87 (m, 8H), 5.21 (s, 2H), 3.90 (s, 3H), 3.51 (s, 3H), 3.46–3.39 (m, 1H), 2.74–2.72 (m, 2H), 2.16–1.59 (m, 5H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 157.8, 149.2, 142.9, 139.5, 129.8, 129.3, 129.0, 126.3, 122.9, 120.9, 120.3, 115.3, 113.9, 107.2, 94.7, 78.2, 77.3, 56.3, 46.9, 38.6, 37.9, 29.9, 28.5, 27.6, 23.4, 20.1, 14.5; HRMS (ES+) calcd for $\text{C}_{27}\text{H}_{34}\text{O}_5$ ($\text{M}+\text{H}$) $^+$, 439.2484; found 439.2475.

7-{2-[4-(3,7-Dimethyl-octa-6,7-dienyl)-phenyl]-vinyl}-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (39). To a suspension of NaH (64 mg, 1.6 mmol, 60% in mineral oil) in THF (17 mL) at 0 °C was added a mixture of phosphonate **26** (56 mg, 0.15 mmol) and aldehyde **12** (28 mg, 0.09 mmol) in THF (3 mL). After 5 min 15C5 (10 μ L) was added and the reaction was allowed to warm to rt and stir for 19 hr. Water was added and the mixture was extracted with ethyl acetate. The combined organic phase was washed with brine and dried (MgSO₄). Concentration in vacuo afforded a yellow oil and final purification by column chromatography (1:1 hexanes:EtOAc) gave the stilbene **39** (26 mg, 55%) as a clear oil: ¹H NMR δ 7.40 (m, 2H), 7.16 (m, 2H), 6.95 – 6.94 (m, 2H), 6.89 – 6.88 (m, 2H), 5.34 (td, J = 7.3, 1.0 Hz, 1H), 5.11 (t, J = 6.7 Hz, 1H), 3.89 (s, 3H), 3.43 (dd, J = 11.7, 4.0 Hz, 1H), 3.35 (d, J = 7.3 Hz, 2H), 2.74 – 2.71 (m, 2H), 2.16 – 2.04 (m, 5H), 1.90 – 1.81 (m, 2H), 1.80 – 1.70 (m, 2H), 1.71 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.25 (s, 3H), 1.10 (s, 3H), 0.90 (s, 3H); ¹³C NMR δ 148.9, 142.5, 140.9, 136.3, 135.2, 131.4, 129.1 (2C), 128.6, 127.8, 126.2, 126.2 (2C), 124.2, 122.8, 122.6, 120.4, 106.9, 78.0, 77.0, 56.0, 46.7, 39.7, 38.4, 37.6, 33.9, 28.3, 27.3, 26.6, 25.7, 23.1, 19.8, 17.7, 16.1, 14.3; HREIMS calcd for C₃₅H₄₆O₃ (M⁺) 514.3447, found 514.3447.

7-{2-[4-(3,7-Dimethyl-octa-2,6-dienyl)-3,5-difluoro-phenyl]-vinyl}-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (40) To a stirred suspension of NaH (30 mg, 1.3 mmol) and 15C5 (5 μ L, 3 mol %) in THF (5 mL) was added phosphonate **29** (71 mg, 0.177 mmol) and aldehyde **12** (20 mg, 0.066 mmol) at 0 °C and the solution was allowed to warm to rt over 10 h. The reaction was quenched by addition of water and then was extracted with EtOAc. The combined organic layers were washed

with brine, dried (MgSO₄), and concentrated *in vacuo*. Final purification of the residue by flash column chromatography (50% EtOAc in hexanes) afforded compound **40** (30.9 mg, 85%) as a clear oil: ¹H NMR δ 6.99–6.79 (m, 6H), 5.26–5.22 (tm, *J* = 7.0 Hz, 1H), 5.09–5.04 (tm, *J* = 6.8 Hz, 1H), 3.9 (s, 3H), 3.47–3.42 (m, 1H), 3.37–3.35 (dm, *J* = 7.2 Hz, 2H), 2.77–2.74 (m, 1H), 2.73–2.70 (m, 1H), 2.18–1.82 (m, 7H), 1.76 (s, 3H), 1.72–1.69 (m, 2H), 1.65 (s, 3H), 1.58 (s, 3H), 1.27 (s, 3H), 1.09 (s, 3H), 0.90 (s, 3H); ¹³C NMR δ 163.4–160.0 (dd, *J*_{CF} = 241.8 Hz, *J*_{CF} = 9.8 Hz, 2C), 149.3, 143.4, 137.9, 136.8, 131.7, 130.5, 124.5 (t, *J*_{CF} = 9.5 Hz), 124.3, 123.0, 121.1, 120.8, 115.9 (t, *J*_{CF} = 23.4 Hz), 110.0, 108.7 (dd, *J*_{CF} = 26.6 Hz, *J*_{CF} = 8.6 Hz, 2C), 107.3, 78.2, 77.4, 56.3, 47.0, 39.8, 38.6, 37.9, 28.5, 27.6, 26.7, 25.8, 23.4, 21.6 (t, *J*_{CF} = 2.0 Hz), 20.1, 17.8, 16.2, 14.5; HRMS (EI) calcd for C₃₅H₄₄O₃F₂ [M⁺], 550.3259; found 550.3256.

7-{2-[4-(8-Hydroxy-3,7-dimethyl-octa-2,6-dienyl)-3,5-bis-methoxymethoxy-phenyl]-vinyl}-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (41) To a suspension of NaH (12 mg, 0.3 mmol) and 15C5 (5 μL, 3 mol %) in THF (5mL) was added phosphonate **35** (34 mg, 0.068 mmol) and aldehyde **12** (16 mg, 0.053 mmol) at 0 °C and the reaction mixture was allowed to warm to rt over 10 h. The reaction was quenched by addition of water and extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), and concentrated *in vacuo*. Purification of the resulting oil by flash column chromatography (50% EtOAc in hexanes) afforded compound **41** (20.5 mg, 60%) as a clear oil: ¹H NMR δ 6.99–6.87 (m, 6H), 5.37–5.33 (tm, *J* = 6.0 Hz, 1H), 5.24–5.18 (m, 5H), 3.95 (s, 2H), 3.91 (s, 3H), 3.52–3.39 (m, 9H), 2.74–2.72 (m, 1H), 2.72–2.70 (m, 1H), 2.17–1.98 (m, 5H), 1.90–1.57 (m, 10H), 1.26 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ¹³C NMR δ 156.1 (2C), 149.2, 142.8, 137.0, 134.9,

134.4, 129.1, 128.6, 126.6, 126.2, 123.3, 122.8, 120.8, 119.7, 107.1, 106.3 (2C), 94.8 (2C), 78.3, 77.4, 69.2, 56.2 (2C), 47.0, 39.6, 38.6, 37.9, 28.5, 27.6, 26.3, 23.4, 22.9, 20.1, 16.3, 14.5, 14.3, 13.9; HRMS (EI) calcd for $C_{39}H_{54}O_8 [M^+]$, 650.3819; found 650.3812.

5-Methoxy-1,1,4a-trimethyl-7-styryl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (42)

To a suspension of NaH (26 mg, 1 mmol) and 15C5 (5 μ L, 3 mol %) in THF (5 mL) was added phosphonate **36** (25 mg, 0.12 mmol) and aldehyde **12** (15.8 mg, 0.05 mmol) at 0 $^{\circ}$ C and the reaction mixture was stirred for 10 h at rt. The reaction was quenched by addition of water and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification of the residue by flash column chromatography (35% EtOAc in hexanes) afforded compound **42** (17 mg, 90%) as a clear oil: 1H NMR δ 7.50–7.47 (m, 2H), 7.37–7.34 (m, 2H), 7.26–7.20 (m, 1H), 6.98 (d, J = 8.5 Hz, 2H), 6.91–6.87 (m, 2H), 3.90 (s, 3H), 3.46–3.41 (m, 1H), 2.77–2.75 (m, 1H), 2.72–2.68 (m, 2H), 2.16–2.11 (m, 1H), 1.90–1.81 (m, 2H), 1.74–1.55 (m, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 149.2, 142.9, 137.9, 129.2, 128.9 (2C), 128.8, 127.4, 126.5, 126.4 (2C), 122.9, 120.8, 107.2, 78.2, 77.3, 56.3, 47.0, 38.6, 37.9, 28.5, 27.6, 23.4, 20.1, 14.5; HRMS (EI) calcd for $C_{25}H_{30}O_3 [M^+]$, 378.2195; found 378.2195.

5-[2-(7-Hydroxy-4-methoxy-8,8,10a-trimethyl-5,7,8,8a,9,10a-hexahydro-6H-

xanthen-2-yl)-vinyl]-benzene-1,3-diol (43) To a stirred solution of stilbene **37** (30 mg, 0.06 mmol) in methanol (5 mL) was added CSA (20 mg, 0.09 mmol) and the solution was allowed to stir 10 h at 50 $^{\circ}$ C. The reaction mixture was allowed to cool to rt, concentrated *in vacuo*, and the residue was dissolved in EtOAc and water. The mixture was extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*.

Final purification of the residue by flash column chromatography (60% EtOAc in hexanes) afforded compound **43** (23 mg, 93%) as a clear oil: ^1H NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 7.06–6.88 (m, 4H), 6.58 (d, $J = 2.0$ Hz, 2H), 6.31 (t, $J = 2.0$ Hz, 1H), 3.97 (s, 3H), 3.75–3.68 (m, 1H), 2.96–2.81 (m, 2H), 2.20–1.68 (m, 5H), 1.33 (s, 3H), 1.16 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 157.7 (2C), 148.3, 142.0, 139.4, 128.8, 128.0, 125.9, 122.3, 120.3, 106.6, 104.3 (2C), 101.2, 77.0, 76.7, 55.1, 46.9, 37.8, 37.2, 27.2, 26.2, 22.5, 18.9, 13.4; HRMS (EI) calcd for $\text{C}_{25}\text{H}_{30}\text{O}_5$ [M^+], 410.2093; found 410.2093.

7-[2-(3-Hydroxy-phenyl)-vinyl]-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (44) CSA (17 mg, 0.073 mmol) was added to a stirred solution of stilbene **38** (16 mg, 0.036 mmol) in methanol (5 mL) and the reaction mixture was allowed to stir for 15 h at rt. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc and water. The mixture was extracted with ether, the organic layer was washed with brine, dried (MgSO_4), and concentrated *in vacuo*.

Purification of the residue by flash column chromatography (60% EtOAc in hexanes) afforded compound **44** (9 mg, 63%) as a clear oil: ^1H NMR δ 7.26–7.19 (m, 1H), 7.06–6.85 (m, 6H), 6.73–6.70 (m, 1H), 5.05 (s, 1H, exchangeable with D_2O), 3.83 (s, 3H), 3.46–3.43 (m, 1H), 2.75–2.66 (m, 2H), 2.18–1.61 (m, 5H), 1.49 (br. s, 1H, exchangeable with D_2O), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR δ 156.1, 149.2, 142.9, 139.6, 130.0, 129.4, 129.0, 126.1, 122.9, 120.9, 119.3, 114.4, 112.9, 107.2, 78.3, 77.4, 56.2, 46.9, 38.6, 37.8, 28.5, 27.6, 23.4, 20.1, 14.5; HRMS (EI) calcd for $\text{C}_{25}\text{H}_{30}\text{O}_4$ ($\text{M}+\text{H}^+$), 395.2222; found 395.2237.

2-(8-Hydroxy-3,7-dimethyl-octa-2,6-dienyl)-5-[2-(7-hydroxy-4-methoxy-8,8,10a-trimethyl-5,7,8,8a,9,10a-hexahydro-6H-xanthen-2-yl)-vinyl]-benzene-1,3-diol (45)

CSA (20 mg, 0.09 mmol) was added to a stirred solution of stilbene **41** (17 mg, 0.026 mmol) in methanol (5 mL) and the reaction mixture was allowed to stir for 15 h at 50 °C. The reaction mixture was allowed to cool to rt, and concentrated *in vacuo* and the residue was dissolved in EtOAc and water. The mixture was extracted with ether, the organic layer was washed with brine, dried (MgSO₄), and concentrated *in vacuo*. Purification of the residue by flash column chromatography (80% EtOAc in hexanes) afforded compound **45** (6 mg, 42%) as a clear oil: ¹H NMR δ 6.94–6.73 (m, 4H), 6.49 (s, 2H), 5.40 (s, 2H, exchangeable with D₂O), 5.31–5.29 (m, 2H), 4.01 (s, 2H), 3.89 (s, 3H), 3.45–3.43 (m, 3H), 2.74–2.72 (m, 1H), 2.72–2.70 (m, 1H), 2.37–2.12 (m, 5H), 1.91–1.57 (m, 10H), 1.46 (s, 1H, exchangeable with D₂O), 1.26 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ¹³C NMR δ 155.2 (2C), 149.2, 142.9, 139.2, 137.6, 136.5, 129.0 (2C), 125.8, 125.0, 122.9, 122.7, 120.8, 112.6, 107.2, 106.4 (2C), 78.1, 69.1, 56.2, 47.0, 39.4, 38.6, 37.9, 28.4, 27.6 (2C), 25.1, 23.4, 22.7, 20.1, 15.8, 14.5, 13.9; HRMS (EI) calcd for C₃₅H₄₆O₆ [M⁺], 561.3216; found 561.3214.

Acknowledgements.

Financial support from the Breast Cancer Research Program (DAMD17-01-1-0276 and DAMD17-02-1-0423), the University of Iowa Graduate College, and an Oncology Research Training Award from the Holden Comprehensive Cancer Center's Institutional National Research Service Award (2 T32 CA79445-05) is gratefully acknowledged.

References

- (1) a) Cytotoxic geranyl stilbenes from *Macaranga schweinfurthii*. Beutler, J. A.; Shoemaker, R. H.; Johnson, T.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 1509-1512. b) Schweinfurthin D, a cytotoxic stilbene from *Macaranga schweinfurthii*. Beutler, J. A.; Jato, J.; Cragg, G. M.; Boyd, M. R. *Nat. Prod. Lett.* **2000**, *14*, 399-404.
- (2) Plants of New-Caledonia .140. Vedelianin, a Hexahydroxanthene Derivative Isolated from *Macaranga-Vedeliania*. Thoison, O.; Hnawia, E.; Guerittevoegelein, F.; Sevenet, T. *Phytochemistry* **1992**, *31*, 1439-1442.
- (3) a) An information-intensive approach to the molecular pharmacology of cancer. Weinstein, J. N.; Myers, T. G.; OConnor, P. M.; Friend, S. H.; Fornace, A. J.; Kohn, K. W.; Fojo, T.; Bates, S. E.; Rubinstein, L. V.; Anderson, N. L.; Buolamwini, J. K.; vanOsdol, W. W.; Monks, A. P.; Scudiero, D. A.; Sausville, E. A.; Zaharevitz, D. W.; Bunow, B.; Viswanadhan, V. N.; Johnson, G. S.; Wittes, R. E.; Paull, K. D. *Science* **1997**, *275*, 343-349. b) Display and Analysis of Patterns of Differential Activity of Drugs against Human-Tumor Cell-Lines - Development of Mean Graph and Compare Algorithm. Paull, K. D.; Shoemaker, R. H.; Hodes, L.; Monks, A.; Scudiero, D. A.; Rubinstein, L.; Plowman, J.; Boyd, M. R. *J. Natl. Cancer Inst.* **1989**, *81*, 1088-1092.
- (4) Paull, K. D. In *Cancer chemotherapeutic agents*; Foye, W. O., Ed.; American Chemical Society: Washington, DC, **1995**, p 9-44. a) Mining the National Cancer Institute's tumor-screening database: Identification of compounds with similar cellular activities. Rabow, A. A.; Shoemaker, R. H.; Sausville, E. A.; Covell, D. G. *J. Med. Chem.* **2002**, *45*, 818-840.

- (5) Phosphonate and bisphosphonate analogues of farnesyl pyrophosphate as potential inhibitors of farnesyl protein transferase. Holstein, S. A.; Cermak, D. M.; Wiemer, D. F.; Lewis, K.; Hohl, R. J. *Bioorg. Med. Chem.* **1998**, *6*, 687-694.
- (6) Treadwell, E. M. Doctor of Philosophy, University of Iowa, 2001. a) Arieianal, a prenylated benzoic acid from *Piper arieianum*. Green, T. P.; Treadwell, E. M.; Wiemer, D. F. *J. Nat. Prod.* **1999**, *62*, 367-368.
- (7) Synthesis of Schweinfurthin C, a geranylated stilbene from *Macaranga schweinfurthii*. Treadwell, E. M.; Cermak, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718-8723.
- (8) a) A short enantioselective total synthesis of dammarenediol II. Corey, E. J.; Lin, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 8765-8766. b) A simple enantioselective synthesis of the biologically active tetracyclic marine sesterterpene scalarenediol. Corey, E. J.; Luo, G. L.; Lin, L. S. Z. *J. Am. Chem. Soc.* **1997**, *119*, 9927-9928. c) Exceptionally simple enantioselective syntheses of chiral hexa- and tetracyclic polyprenoids of sedimentary origin. Corey, E. J.; Luo, G. L.; Lin, L. U. S. Z. *Angew. Chem.-Int. Edit.* **1998**, *37*, 1126-1128. d) A simple enantioselective synthesis of serratenediol. Zhang, J. H.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215-3216. and references cited there in.
- (9) A cascade cyclization approach to schweinfurthin B. Treadwell, E. M.; Neighbors, J. D.; Wiemer, D. F. *Org. Lett.* **2002**, *4*, 3639-3642.
- (10) 2,3-Oxidosqualene, an Intermediate in the Biological Synthesis of Sterols from Squalene. Corey, E. J.; Russey, W. E.; Ortiz de Motellano, P. R. *Journal of American Chemical Society* **1966**, *88*, 4750-4751. a) Enzymic conversion of squalene

2,3-oxide to lanosterol and cholesterol. van Tamelen, E. E.; Willett, J. D.; Clayton, R. B.; Lord, K. E. *J. Am. Chem. Soc.* **1966**, *88*, 4752-4.

(11) An Epoxide-Initiated Cascade Cyclization Approach to the Schweinfurthins: Synthesis of 3-Deoxyschweinfurthin B. Neighbors, J. D. *J. Org. Chem.* **2005**, *70*, 925-931.

(12) a) Inhibitors of NF-kappa B signaling: Design and synthesis of a biotinylated isopanepoxydone affinity reagent. Shotwell, J. B.; Koh, B.; Choi, H. W.; Wood, J. L.; Crews, C. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3463-3466. b) Total synthesis of a biotinylated derivative of phorbaxazole A via sonogashira coupling. Hansen, T. M.; Engler, M. M.; Forsyth, C. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2127-2130.

(13) Total synthesis of pawhuskin C: a directed ortho metalation approach. Neighbors, J. D.; Wiemer, D. F.; Salinkova, M. *Tetrahedron Lett.* **2005**, *46*, 1321-1324.

(14) A Convenient Modification of the Wadsworth-Emmons Method of Olefin Formation Using a Crown Ether. Baker, R.; Sims, R. J. *Synthesis* **1981**, 117-117.

(15) Methoxymethyl-Directed Aryl Metalation - a Total Synthesis of (+/-)-Averufin. Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885-6888.

(16) a) Regioselective Metalation Reactions of Some Substituted (Methoxymethoxy)Arenes. Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101-2108. b) Regioselective Metallations of (Methoxymethoxy)Arenes. Ronald, R. C.; Winkle, M. R. *Tetrahedron* **1983**, *39*, 2031-2042.

- (17) An Efficient Route to S-N-(9-Fluorenylmethoxycarbonyl)-4'-(1-Azi-2,2,2-Trifluoroethyl)Phenylalanine. Fishwick, C. W. G.; Sanderson, J. M.; Findlay, J. B. C. *Tetrahedron Lett.* **1994**, 35, 4611-4614.
- (18) Rhodium Carbenoid Mediated Cyclizations .4. Synthetic Approaches to Oxepanes Related to Zoapatanol. Davies, M. J.; Heslin, J. C.; Moody, C. J. *J. Chem. Soc.-Perkin Trans. 1* **1989**, 2473-2484.
- (19) The first direct synthesis of alpha-mangostin, a potent inhibitor of the acidic sphingomyelinase. Iikubo, K.; Ishikawa, Y.; Ando, N.; Umezawa, K.; Nishiyama, S. *Tetrahedron Lett.* **2002**, 43, 291-293.

Table of Contents graphic:

